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Original Communications

THE EFFECT OF VARIOUS SUPPLEMENTS TO THE DIET ON THE IRON BALANCE OF THE ANEMIC INFANT

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IN AN earlier report on the influence of fruit and vegetable feeding upon the iron metabolism of the infant we included a study of the iron balance of one infant suffering from nutritional anemia. The results showed that, while addition of dried spinach to a milk diet caused a lowered retention of iron, the further addition of apricots caused a marked increase in the retention of iron. The iron retention was also increased by feeding large amounts of iron in the form of ferric ammonium citrate. It showed a further increase when an additional supplement of liver was made to the diet. In spite of the increased retention of iron, the hemoglobin concentration of the blood was not improved until the iron salt in the diet was supplemented by liver.

To determine whether these results were peculiar to the individual case or typical also of other cases of secondary anemia in infants, we have continued the study of the effects of these foods on the iron retentions of three other anemic infants.

The three infants, J. H., G. K., and R. K. were thirteen, eight, and eight months old, respectively, when the metabolism study was begun.

EXPERIMENTAL PROCEDURE

The same general plan was followed in the study of these cases as in the case reported previously. With the exception of the control periods on powdered milk,* cane sugar, and cod liver oil, the infants

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*Powdered milk in the form of dryco was furnished through the courtesy of the Dry Milk Company.

received each diet for a period of at least fifteen days before an additional supplement to the diet was made. Care was taken to keep the supplements as uniform as possible, and the daily amount of each,* with the exception of the iron salts, was constant for all three cases. After the infant had received a given diet for a fore period of at least five days, the urine and feces were collected for two consecutive periods of five days each, aliquots of food, urine, and feces were analyzed for iron content and the iron balance calculated.

Supplements to the diets were not made in the same order for each infant. In every case the first period was a control on powdered milk, cane sugar, and cod liver oil formula. Following the control period, J. H. and G. K. were given puréed spinach for periods 2 and 3. This particular form of spinach was used as it had been found to be utilized slightly better by normal infants than either the dried or raw form.[1] During periods 4 and 5 J. H. and G. K. received both spinach and apricots. R. K. was given apricots during periods 2 and 3 and apricots and puréed spinach in periods 4 and 5. It was felt that, if a greater percentage of the iron of apricots than of spinach were retained, it would be reflected in his iron balance when compared with that of the other two infants.

An intestinal disturbance, accompanied by diarrhea, occurred in the case of infant J. H. after period 5 and the study was discontinued for a short time. It was not felt that the diet had caused this disturbance as the same foods had been given to several other infants with no evidence of diarrhea.

After recovery, J. H. was given a basic formula of powdered milk, cane sugar, orange juice, and cod liver oil during period 6. This diet was supplemented with liver during periods 7 and 8 and further supplemented with varying amounts of iron salts (111 to 199 mg.) in the form of ferrous sulphate in glucose solution during the four periods following. It seemed of interest to compare the effect of the ferrous salt with that of the ferric form, since Lottrup[2, 3] and Parsons and Hawksley[4] had found ferrous salts more effective in curing secondary anemias. In periods 13 and 14 copper in the form of cupric sulphate was given as an additional supplement to the liver and the iron salts.

Spinach and apricots were continued in the diet of G. K. and R. K. throughout the remainder of the study. In the case of G. K. further supplements of ferric ammonium citrate (132 to 146 mg. Fe), cupric sulphate, and liver were given in the order mentioned. In the diet of R. K. the same supplements were given, but the order was cupric sulphate, ferric ammonium citrate, and, finally, liver.

*Puréed spinach was supplied through the courtesy of Van Camp's Inc. Daily supplements of 70 gm. were given. Daily supplements of apricots were equivalent to 40 gm. of the dried fruit. Daily supplements of calf's liver amounted to 20 gm. Twelve milligrams of copper, as copper sulphate, were given daily.

Details concerning the preparation of food, the collection of excreta and the methods used for determining iron and hemoglobin have been given in the previous communication.

All three infants were in positive nitrogen balance and each showed consistent weight gains during every period studied. Feedings were taken well, and with the exception of the anemia the infants seemed to be quite normal. In all cases the anemias were thought to have been caused by inadequate diets and were therefore believed to be comparable.

HISTORY OF CASES

CASE 1.—J. H., a male infant, was a full-term baby, delivered by low forceps with no complications. Birth weight was 3,790 gm. The baby was normal except for a bilateral harelip and a unilateral cleft palate. Feeding consisted of breast milk and dryco, by gavage. Cod liver oil and viosterol were given regularly. He was first brought to this clinic at the age of one month, in good nutritive state. An operation was performed, and the harelip was repaired. During his first year he had measles and two acute attacks of otitis media (left). He was readmitted to the hospital at the age of one year, a well-nourished and well-developed child, for repair of the cleft palate. His hemoglobin at the time of admittance was 70 per cent. During his convalescence, his hemoglobin fell to 40 per cent, and at the age of thirteen months he was diagnosed as having secondary anemia.

CASE 2.—G. K., a male infant, was one of identical, full-term twins. His birth history was normal, and his birth weight was 2,355 gm. He was first seen at this clinic at the age of eight months, when he was brought in because of irritability and paleness. He had been breast fed for the first two months of life and then was given complementary feedings until the fourth month, at which time he was given a formula consisting of whole milk, cane sugar, and water. Cod liver oil and orange juice were given regularly after the second month, but cereals and vegetables were not introduced into his diet until he was seven months old. The child had been in fair health and had suffered from no contagious diseases. Upon admission his hemoglobin was found to be 44 per cent, and the case was diagnosed as secondary anemia.

CASE 3.—R. K., a male infant, was first seen at this clinic at the age of eight months. He was the identical twin of G. K., and birth had been normal. Birth weight was 2,540 gm. His feeding since birth had been the same as that of G. K. which has been described previously. He had always been in apparent good health and had suffered from no contagious diseases. He was brought to the clinic because of a noticeable pallor and an acute upper respiratory infection. A hemoglobin value of 37 per cent was found, and the case was diagnosed as one of secondary anemia.

DISCUSSION OF RESULTS

The iron intakes and retentions and the corresponding hemoglobin values for these cases as influenced by the various supplements to the diets will be found in Charts 1 and 2.

Effect of Spinach.—The addition of puréed spinach to the control diet of infants J. H. and G. K. caused a very small increase in the retention of iron in one case and a very slight decrease in the other.

When added to the control diet supplemented with apricots, in the case of R. K., the retention remained the same as on the milk-apricot diet. The hemoglobin showed no appreciable change in any case.

The addition of dried spinach resulted in a negative iron balance in the case of secondary anemia reported previously. No negative balances were found in these cases when the puréed form was used. However, the additional iron given in this form did not appear to be retained. It would seem that anemic infants are not able to utilize the iron of spinach.

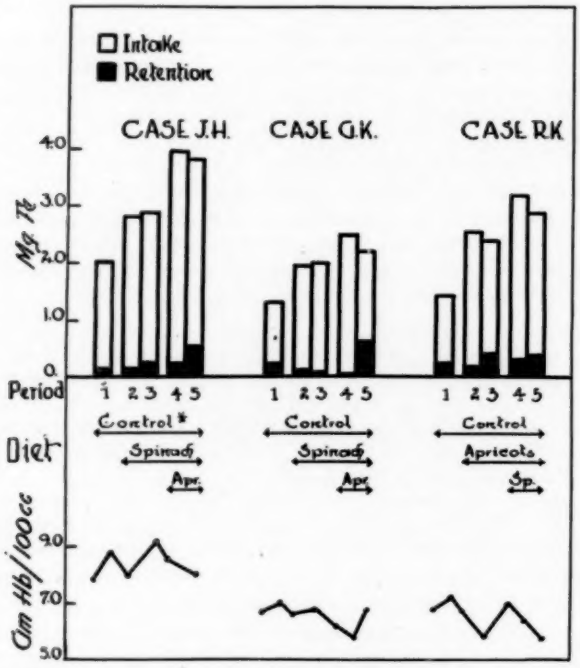

Chart 1.—The effect of spinach and apricot feeding on the retention of iron and the formation of hemoglobin.

*Control diet: Powdered milk, cane sugar, and cod liver oil.

Effect of Apricots.—When apricots were added to a milk-spinach diet (J. H. and G. K.), the retentions were slightly higher than on either the control or the milk-spinach diet. The addition of apricots to the control diet (R. K.) caused a slightly increased retention which was not increased further by the addition of spinach. The retentions in all cases were small, and the hemoglobin values were not appreciably affected. In no case was there a decrease in the fecal output or a marked increase in the retention as occurred in the case of the infant reported previously.

Since the retention of iron showed a slight increase in all cases when apricots were fed, it would seem that the iron of apricots is more readily available to the anemic infant than that of spinach. This may

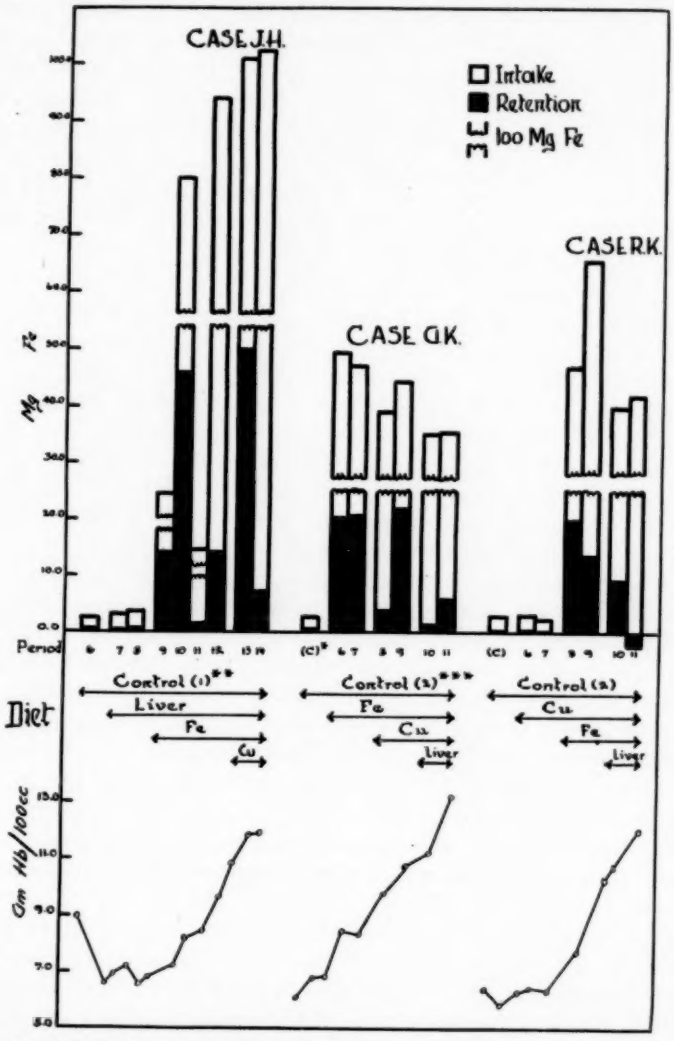

Chart 2.—Effect of iron and copper salts and liver on the retention of iron and the formation of hemoglobin.

*Determined by average results of periods 4 and 5 for each case.
†Control diet (1): Powdered milk, cane sugar, orange juice, and cod liver oil.
‡Control diet (2): Powdered milk, cane sugar, cod liver oil, spinach and apricots.

be due to the fact that a much higher percentage of the iron of apricots than of spinach is in the inorganic form. While we[5] find no conclusive

evidence that a normal child utilizes iron in the inorganic form more readily than in the organic, it is possible that the anemic child might utilize the inorganic portion more easily.

Effect of Iron and Copper Salts Alone and in Combination.—When iron salts in the form of ferric ammonium citrate were added to a diet containing spinach and apricots (G. K.), the retention of iron was increased markedly, and the hemoglobin showed consistent gains. Supplementing this diet further with cupric sulphate did not affect any additional increase in the retention or a more rapid gain in the hemoglobin. It would appear, then, that this infant had been receiving an adequate amount of copper in his previous diets and that iron rather than copper had been the limiting factor.

On the other hand, the addition of copper salts to a diet containing spinach and apricots (R. K.) caused no change in either retention or hemoglobin. At this level of iron intake additional copper had no beneficial effect. It is quite probable that the copper content of the spinach-apricot diet was adequate as was shown in the case of G. K. When the diet was further supplemented with iron salts, there was a marked increase in the retention, comparable to the increase shown when G. K. first received iron salts. The hemoglobin values during these periods showed a decided gain. These results as in the case of G. K. indicate a definite need of infant R. K. for iron.

These infants were able to store large quantities of iron and to convert it to hemoglobin when it was supplied to them in an easily available form and in amounts which greatly exceeded normal intake. In the case reported previously, no rise in hemoglobin occurred on a similar diet, although there was a decided increase in retention. The iron intake was somewhat lower in this case (100 mg. daily), and the possibility must not be overlooked that the higher iron intake may have accounted for the hemoglobin rises and the higher retentions in the cases of G. K. and R. K.

The Effect of Liver Alone and in Combination With Other Supplements.—Liver, when added to a control diet of milk (J. H.), caused a slight increase in the retention similar to the increase found when approximately the same amount of iron in the form of apricots was added to a milk-spinach diet (J. H.). As in the case of the apricots, there was no gain in hemoglobin.

The addition of iron salts in the form of ferrous sulphate to a milk-liver diet (J. H.) brought about a decided increase in retention for three of the four periods studied. The amount of iron given varied from period to period, and the trend of the retention followed the general trend of the intake. The hemoglobin also showed a significant gain during this time. The retention of iron by J. H. when receiving ferrous sulphate was of the same order of magnitude as those of G. K.

and R. K. when given ferric ammonium citrate. There was no evidence from either the iron retention or the hemoglobin formation that ferrous salts were preferable to ferric salts in the case of our infants.

When a further addition of copper salts was made to the liver-iron diet (J. H.), the iron retention during the first period was higher than it has been at previous times, and the rate of gain of hemoglobin was also increased. During the second period on this diet the retention was much lower, while the hemoglobin continued to gain at approximately the same rate. The lowered retention during that period may have been due to a lessened need for iron, since at that time the hemoglobin was approaching a normal value.

There was a definite decrease in the retention in two cases (G. K. and R. K.) when liver was given in conjunction with iron and copper salts, apricots, and spinach. The hemoglobin values at that time, however, were rapidly approaching normal, and again it may be that the lessened need for iron was the real cause for the lowered retention. The hemoglobin continued to rise during these periods at approximately the same rate as formerly.

Our results with J. H., G. K., and R. K. show no evidence that liver was of value in the treatment of their secondary anemias, either when fed alone or in addition to a diet containing spinach, apricots, and iron and copper salts. In the case of the anemic infant previously reported, liver had appeared to be of great benefit since immediately on supplementing the spinach, apricot, and iron and copper salt diet with liver, an increased iron retention and a marked rise in hemoglobin occurred. It may be important in this connection to note that this infant was older (twenty-three months) at the time the metabolism study was begun. His anemia was apparently of much longer standing, and he showed a marked anorexia which was not characteristic of the other infants. The elimination of large hard stools at approximately two-day intervals indicated an intestinal disturbance which may have complicated the results. We believe that the results on J. H., G. K. and R. K. shown in this report represent more nearly the reactions of a simple case of secondary anemia caused by malnutrition.

SUMMARY

The effect of various supplements to the diet on the iron retention and hemoglobin of three cases of secondary anemia has been shown.

Additional iron, when supplied by puréed spinach, was not utilized by these infants.

The iron of apricots, although utilized somewhat better than that of spinach, affected no change in hemoglobin and only a slight increase in retention.

Iron salts, when given in large amounts either in the form of ferrous sulphate or ferric ammonium citrate caused a marked increase in the

retention and a rise in hemoglobin. There was no evidence shown that the ferrous salt was more efficacious than the ferric salt.

Copper salts, given in conjunction with either a low or a high iron intake, did not seem to have any effect on the iron retention or the hemoglobin level. The copper contents of the previous diets were apparently adequate.

The introduction of liver into a diet of low iron content caused a slight increase in retention, but no gain in hemoglobin. With a high iron intake, a decreased retention of iron occurred coincident with the addition of liver to the diet. It is suggested that this lowered retention was due not to the liver per se, but to a lessened need of the infant for iron at that time.

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COMPARATIVE ANTIRACHITIC EFFECTIVENESS OF VIOSTEROL, COD LIVER OIL, AND PERCOMORPH LIVER OIL

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IN 1930 Massengale and Nussmeier,[1] as well as Hess and Supplee,[2] demonstrated that from the standpoint of equivalent rat unit dosage, cod liver oil was many times more effective than viosterol in the prevention of leg weakness in chickens. These observations have been repeatedly confirmed. As a result of the investigations in chickens, it is now generally conceded that the antirachitic factors of cod liver oil and of viosterol are not identical.

Regarding the relative effectiveness of cod liver oil and viosterol in infants, Hess and Lewis[3] stated several years ago that, rat unit for rat unit, cod liver oil is a more effective antirachitic agent than viosterol. Barnes, Brady, and James,[4] as well as DeSanctis and Craig,[5] also arrived at the conclusion that cod liver oil is more effective than viosterol, from the standpoint of rat unitage, in the prevention and cure of infantile rickets.

The contention, however, that cod liver oil is more effective than the equivalent rat unitage of viosterol in infantile rickets has been questioned recently by Drake, Tisdall, and Brown[7] and by Eliot and her coworkers.[8] These investigators carried out prophylactic tests with viosterol and cod liver oil at various levels and reported that there was no difference in the degree of protection afforded by these agents at comparable unitages.

In view of the divergence of findings regarding the relative effectiveness of cod liver oil and viosterol in infants, we decided to reinvestigate this problem and simultaneously to determine the antirachitic value of a new antirachitic preparation, percomorph liver oil. This product is a mixture of oils obtained from the livers of fish belonging to the percomorphi order. Bills and his coworkers[6] have demonstrated that the liver oils of many of the species of the percomorphi group have extremely high concentrations of vitamins A and D and are from fifty to a thousand times more potent than cod liver oil in these vitamins. If cod liver oil is more effective than the same rat unitage of viosterol, we thought it would be of interest to know which of these agents percomorph liver oil more closely resembles in its activity.

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This investigation was aided by a grant from the Mead Johnson Company, Evansville, Indiana.

Accordingly, it was planned to prescribe viosterol, cod liver oil, and percomorph liver oil at comparable levels to large groups of young infants during the winter, and to compare the incidence of rickets among these various groups. In addition, it was decided to compare the curative effects of these antirachitic agents on infants manifesting rickets by roentgenologic examination.

This investigation was carried out in the Infant Welfare Stations of the New York City Department of Health, and I wish to take this opportunity of thanking the commissioner, Dr. John L. Rice, for his cooperation.

During November and December infants ranging in age from two weeks to five months were examined for clinical evidences of rickets. Those infants manifesting enlargement of the costochondral junctions were roentgenographed to determine whether rickets was present. The unreliability of diagnosing rickets merely by enlargement of the costochondral junctions has been emphasized previously, since in the majority of such instances rickets cannot be demonstrated by roentgenologic or chemical criteria. On the other hand, the absence of enlargement of the costochondral junctions usually denotes the absence of rickets. Infants who manifested rickets by roentgenologic examination were excluded from the prophylactic groups.

Four hundred and eighty-seven infants who showed no demonstrable enlargement of the costochondral junctions, or who had no evidences of rickets by roentgenologic examination were divided among the following groups:

Group 1. Infants to receive 135 U.S.P. units of viosterol daily.
Group 2. Infants to receive 135 U.S.P. units of cod liver oil daily.
Group 3. Infants to receive 135 U.S.P. units of percomorph liver oil daily.
Group 4. Infants to receive 435 U.S.P. units of viosterol daily.
Group 5. Infants to receive 435 U.S.P. units of cod liver oil daily.
Group 6. Infants to receive 435 U.S.P. units of percomorph liver oil daily.
Group 7. Infants to receive 870 U.S.P. units of percomorph liver oil daily.
Group 8. Infants to serve as controls.

Viosterol and percomorph liver oil were administered by means of special droppers, and the potency of the solutions of these antirachitic agents was adjusted in such a manner that 8 drops contained the requisite number of units.* Mothers were instructed to add 8 drops of these preparations to one-half teaspoonful of orange juice. Cod liver oil,

*The biological assays of the various preparations were carried out by Dr. Charles E. Bills.

diluted with corn oil so that one teaspoonful furnished the required number of units, was given once daily. Teaspoons of a capacity of 4 c.c. were distributed to the mothers, to be used for the administration of the diluted cod liver oil. All infants were carefully followed in the clinic at intervals of approximately three weeks and were visited frequently in their homes by two nurses who were experienced in social service work. Babies whose mothers were not cooperative were immediately eliminated from this investigation.

At the end of March and during April roentgenograms of the wrists were ordered for all infants in order to determine the incidence of rickets among the various groups. In some instances final roentgenograms were taken during the early part of May. Of 487 infants who were originally included in this study 365 were roentgenographed at the end of the investigation, the remainder either having been eliminated for various reasons, or having failed to appear for roentgenologic examination. Of 365 infants, 265, or 73 per cent, were negroes. Table I illustrates the distribution of these 365 infants among the various

TABLE I

ANALYSIS OF THE VARIOUS GROUPS OF INFANTS WITH RESPECT TO THE NUMBER OF INFANTS IN EACH GROUP, AVERAGE AGE, COLOR, SEX, AVERAGE GAIN IN WEIGHT DURING THE COURSE OF STUDY, AND TYPE OF FEEDING

GROUP	ANTIRACHITIC AGENT	NUMBER OF UNITS DAILY	NUMBER OF INFANTS IN EACH GROUP	AVERAGE AGE AT BEGINNING OF STUDY (MONTHS)	NUMBER OF NEGRO INFANTS	PERCENTAGE OF NEGRO INFANTS	PERCENTAGE OF MALE AND FEMALE INFANTS		AVERAGE MONTHLY GAIN IN WEIGHT	NUMBER OF BREAST-FED INFANTS	NUMBER OF BOTTLE-FED INFANTS	NUMBER OF INFANTS RECEIVING BOTH BREAST AND BOTTLE FEEDINGS
							MALE	FEMALE				
1.	Viosterol	135	50	2.9	33	66	58	42	1.3	18	18	14
2.	Cod liver oil	135	50	2.9	38	76	52	48	1.5	7	18	25
3.	Percomorph liver oil	135	46	3.0	37	80	42	58	1.2	9	18	19
4.	Viosterol	435	58	2.6	39	67	56	44	1.4	11	23	24
5.	Cod liver oil	435	51	2.7	39	76	45	55	1.4	14	14	23
6.	Percomorph liver oil	435	39	2.8	27	69	55	45	1.4	8	12	19
7.	Percomorph liver oil	870	50	2.6	36	72	51	49	1.4	6	22	22
8.	Controls	-	21	2.3	16	76	57	43	1.3	6	7	8

groups, the average age of infants in each group, the percentage of negroes, the percentage of male and female infants, the average gain in weight during the course of the study, and the number of breast-fed and artificially fed infants. It will be seen that the groups were quite comparable.

RESULTS OF THE PROPHYLACTIC STUDY

The results of the prophylactic study may be observed in Table II. Of 21 infants receiving no antirachitic agent during the winter months, 13, or 62 per cent, developed roentgenologic evidences of rickets. Since 11 of the 13 rachitic infants were negroes, the incidence of rickets among 16 negroes in the control group was 70 per cent.

TABLE II

COMPARISON OF THE INCIDENCE OF RICKETS AMONG INFANTS RECEIVING VIOSTEROL, COD LIVER OIL, OR PERCOMORPH LIVER OIL

GROUP	ANTIRACHITIC AGENT	NO. OF UNITS DAILY	NO. OF INFANTS IN EACH GROUP	NO. OF INFANTS WHO DEVELOPED RICKETS	DEGREE OF RICKETS		
					MILD	MODERATE	SEVERE
1.	Viosterol	135	50	1	0	1	0
2.	Cod liver oil	135	50	1	0	1	0
3.	Percomorph liver oil	135	46	1	1	0	0
4.	Viosterol	435	58	1	1	0	0
5.	Cod liver oil	435	51	1*	0	1	0
6.	Percomorph liver oil	435	39	0	0	0	0
7.	Percomorph liver oil	870	50	0	0	0	0
8.	Controls	-	21	13	5	8	0

*This infant regurgitated most of the cod liver oil.

Regarding the results with viosterol, it may be noted that rickets developed in one of 50 infants in the 135 unit group and in one of 58 infants receiving 435 units daily. The high degree of protection afforded by viosterol, at levels which have been regarded as being considerably below the protective dose, seems most surprising. It may be recalled that the generally recommended dosage of viosterol for prophylactic purposes is eight to ten drops daily; in other words, approximately from 1,760 to 2,200 U.S.P. units. In this connection it should be added that Tisdall and his coworkers[7] have also found that small doses of viosterol, as, for example, 270 units of viosterol daily, protect most infants against rickets.

Of 50 infants receiving 135 units of cod liver oil daily, one manifested rickets of moderate degree. A moderate degree of rickets occurred also in one of 51 infants receiving 435 units daily. However, since this baby regurgitated most of the oil, the failure in this instance cannot be ascribed directly to cod liver oil.

Of 46 infants receiving 135 units of percomorph liver oil daily, only one developed rickets, the degree of which was mild. Infants receiving 435 and 870 units, respectively, showed no evidences of rickets on roentgenologic examination.

It is apparent that the prophylactic tests do not indicate any significant difference in the effectiveness of viosterol, cod liver oil, and percomorph liver oil, unit for unit, at levels of 135 and 435 U.S.P. units. The results obtained with cod liver oil and viosterol are, therefore, in agreement with those reported by Drake, Tisdall, and Brown and by Eliot, who, as previously stated, found no distinction in the effectiveness of these agents, in their prophylactic studies.

CURATIVE TESTS

The daily dosage of cod liver oil, viosterol, and percomorph liver oil for the curative test was placed at 435 U.S.P. units. This unitage was selected because it was believed from previous experience that 435 units of viosterol, in other words, the equivalent of approximately two drops of the commercial preparation, would be inadequate to cure most cases of infantile rickets. On the other hand, if cod liver oil or percomorph liver oil were more effective, a healing response or even cure might be brought about at this unitage. Irradiated cholesterol was also employed in the curative study, and the dosage was 435 units daily.*

Fourteen rachitic infants, 13 of whom were negroes, comprised the curative groups. The ages of these infants ranged from three to eight and a half months. Two infants were given viosterol; four, percomorph liver oil; two, cod liver oil; three, irradiated cholesterol, and three served as negative controls. The degree of rickets among these groups of infants was comparable. Roentgenograms were taken at the end of four and eight weeks, and in some instances at the end of ten and twelve weeks in order to determine the degree of healing.

The infants were observed from the end of February until the end of May, at which time the study was terminated because of the lateness of the season. At this point it should be mentioned that it has been our experience that spontaneous healing of rickets does not usually occur in negro infants until the end of May or the early part of June. This situation enables one to carry out curative tests among ambulatory negro patients at a later date than would be permissible in the case of white infants.

The results of the curative study may be observed in Table III. Two infants receiving 435 units of viosterol showed no healing in the roentgenograms after four and eight weeks, and one showed only slight healing after twelve weeks (Figs. 1 and 2). On the other hand, of four infants receiving percomorph liver oil, three showed moderate or marked healing, and one questionable healing at the end of four weeks. The

*Irradiated cholesterol was supplied through the courtesy of the Parke, Davis & Company, Detroit, Mich.

TABLE III

A COMPARISON OF HEALING AMONG RACHITIC INFANTS
BROUGHT ABOUT BY VIOSTEROL, PERCOMORPH LIVER OIL, COD LIVER OIL, AND IRRADIATED CHOLESTEROL

CASE	SEX	COLOR	AGE (MO.)	DATE TREATMENT BEGAN	ANTI-RACHITIC AGENT	NUMBER OF RAT UNITS (NEW U.S.P.) GIVEN DAILY	ROENTGENOLOGIC RICKETS				
							AT ONSET	HEALING AFTER FOUR WEEKS	HEALING AFTER EIGHT WEEKS	HEALING AFTER TEN WEEKS	HEALING AFTER TWELVE WEEKS
M. K.	F.	Negro	6½	2/29	Viosterol	435	Mild	Worse	0	±	+
A. R.	M.	Negro	4½	2/29	Viosterol	435	Mod.	0	0		
E. M.	M.	Negro	4	2/29	Percomorph liver oil	435	Mild	+++	++++		Normal
A. G.	F.	Negro	7	2/29	Percomorph liver oil	435	Mod.	++	++++		Normal
J. J.	F.	Negro	6½	3/27	Percomorph liver oil	435	Mod.	†	+++		
G. A.	M.	Negro	7	4/22	Percomorph liver oil	435	Marked	++			
A. C.	F.*	Negro	8½	4/18	Cod liver oil	435	Mod.	+++	+++±†		
J. S.	M.	Negro	7	4/27	Cod liver oil	435	Mod.	++			
C. R.	M.	White	5	2/29	Irradiated cholesterol	435	Mild	++	Normal		Normal
G. S.	F.	Negro	5	2/29	Irradiated cholesterol	435	Mod.	++	+++		++++
J. C.	M.	Negro	4½	4/11	Irradiated cholesterol	435	Mod.	+++	++++†		
M. R.	M.	Negro	4	2/29	Control	0	Mild	0	0		+
M. O.	F.	Negro	3¾	2/29	Control	0	Mild			Worse	0
M. C.	M.	Negro	3	2/29	Control	0	Mild			Worse	

*This infant had received 135 units of cod liver oil from December 21 to April 17 during which time the rachitic process advanced.
†After six weeks.
+Denotes slight healing.
++Denotes moderate healing.
+++Denotes marked healing.
++++Denotes healed rickets.

latter infant manifested marked healing at the end of eight weeks, and two of the other three infants showed healed rickets at the end of eight weeks, and normal bone structure at the end of twelve weeks (Figs. 3 and 4.)

Fig. 1.—A. R. Absence of healing of rickets with the daily administration of 435 U.S.P. units of viosterol. *A*, February 29 (begun); *B*, April 1; *C*, April 29.

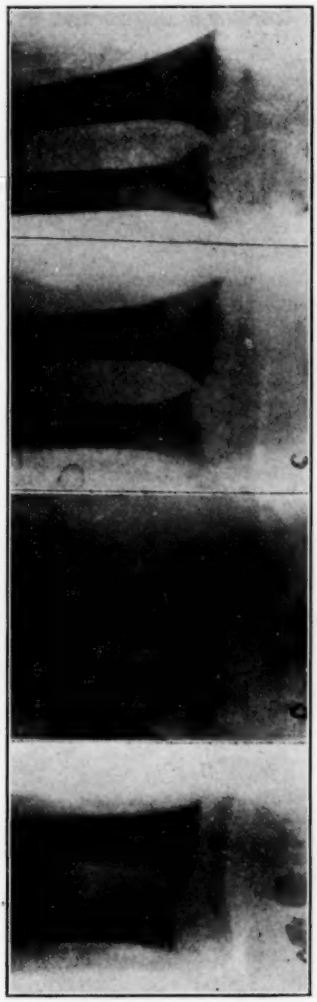


Fig. 2.—M. K. Absence of satisfactory healing of rickets with the daily administration of 435 U.S.P. units of viosterol: *A*, February 29 (begun); *B*, April 1; *C*, May 18; *D*, May 29.

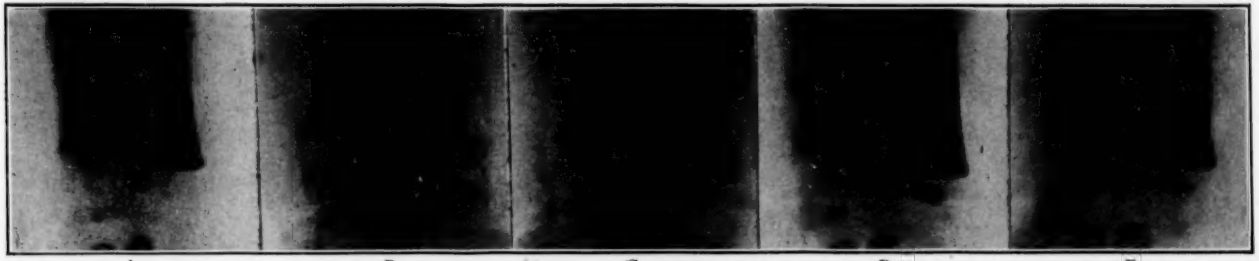
Two infants receiving 435 units of cod liver oil daily manifested moderate or marked healing at the end of four weeks, and after six weeks there was almost healed rickets in one instance. It is of interest to mention that one of these infants had received 135 units of cod liver oil for four months previously and during this time the rachitic process had advanced (Fig. 5).

Curative tests with 435 units of irradiated cholesterol revealed that at the end of four weeks moderate healing occurred in two infants and marked healing in one infant (Fig. 6). At the end of eight weeks healing progressed; in two infants the roentgenograms disclosed normal bone structure or healed rickets.

Fig. 3.—A. G. Healing of rickets brought about by the daily administration of 435 U.S.P. units of percomorph liver oil: *A*, February 29 (begun); *B*, April 4; *C*, April 29; *D*, May 29.

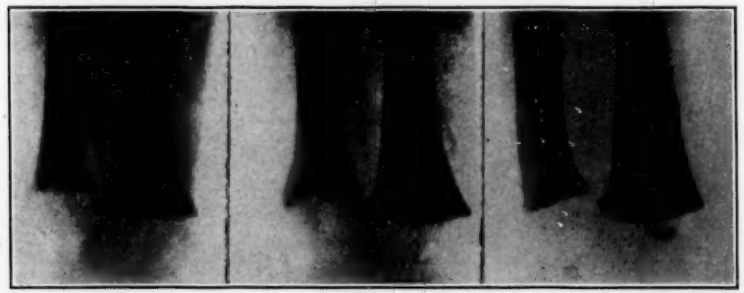
Fig. 4.—E. M. Healing of rickets brought about by the daily administration of 435 U.S.P. units of percomorph liver oil: *A*, February 29 (begun); *B*, April 3; *C*, April 29; *D*, May 29.

Of three infants who served as controls no healing was observed after eight or ten weeks; in one instance slight healing was noted at the end of twelve weeks (Figs. 7 and 8). The paucity of healing in this group indicates that the favorable response observed in the rachitic infants receiving percomorph liver oil, cod liver oil, or irradiated cholesterol was due to the administration of these agents.



A. *B.* *C.* *D.* *E.*

Fig. 5.—A. C. Absence of healing of rickets with the daily administration of 135 units of cod liver oil; rapid healing brought about by 435 U.S.P. units of cod liver oil daily: *A*, December 23, 135 units begun; *B*, April 18, rickets worse, 435 units of cod liver oil begun; *C*, May 15; *D*, May 29; *E*, June 25.



A. *B.* *C.*

Fig. 6.—G. S. Healing of rickets brought about by the daily administration of 435 U.S.P. units of irradiated cholesterol: *A*, February 29 (begun); *B*, March 30; *C*, May 29.

COMMENT

The results of the curative tests seem to indicate that, rat unit for rat unit, cod liver oil, percomorph liver oil, and irradiated cholesterol are more effective antirachitic agents than viosterol. It is significant

Fig. 7.—M. O. Control case. Absence of healing of rickets in infant receiving no antirachitic agent: *A*, February 21; *B*, May 8; *C*, May 29; *D*, June 25.

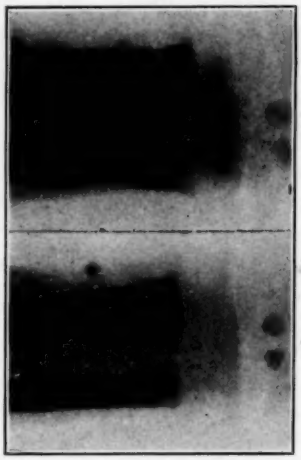


Fig. 8.—M. C. Control case. Absence of healing of rickets in infant receiving no antirachitic agent: *A*, February 21; *B*, May 11.

that cod liver oil, percomorph liver oil, and irradiated cholesterol represent the animal source of vitamin D, whereas viosterol represents the plant source of the antirachitic factor. Waddell and later Bethke and his associates have shown from animal experiments that provitamin D of animal origin and that of plant source are not identical and that from

the standpoint of rat unitage vitamin D of animal origin is from twenty-five to one hundred times more effective than vitamin D of plant source in preventing rachitic manifestations in chickens. The results of our clinical study are in agreement with the chicken-rat findings of Waddell and of Bethke.

It is not possible at this time to state the exact ratio of effectiveness between animal and plant sources of vitamin D in the treatment of infantile rickets as the minimum curative dosage of vitamin D of animal and of plant origin is not known. However, from experiments which have been conducted during the past year and which will soon be published, we have sufficient evidence to lead us to believe that for mild or moderate cases of infantile rickets in negro infants the minimum curative daily dosage of the animal source of vitamin D lies between 270 and 435 U.S.P. units. From reports in the literature and from our own experience concerning the curative dosage of viosterol, one may conclude that the minimum curative dosage of this antirachitic agent for cases of mild or moderate rickets in negro infants is somewhere between 4 and 10 drops; in other words, between 880 and 2,200 U.S.P. units. It would seem, therefore, that from the standpoint of the number of units required to cure mild or moderate cases of infantile rickets, the ratio of effectiveness of vitamin D of animal origin to that of plant origin lies somewhere between 2 to 1 and 8 to 1. As previously stated, the exact ratio can be obtained by determining under similar conditions the minimum curative dosage of vitamin D obtained from animal and from plant sources. However, since the ratio of effectiveness between vitamin D of animal and that of plant origin in preventing rachitic manifestations in chickens is between 25 to 1 and 100 to 1, one can definitely conclude that the effectiveness of vitamin D of animal origin as compared with that of plant source is considerably lower in the infant than it is in the chicken.

It is significant that a distinction between viosterol, and cod liver oil and percomorph liver oil was brought out in the curative test but not in the prophylactic experiment. Of 146 infants receiving only 135 U.S.P. units daily of these antirachitic agents, all but three were protected against rickets. It is possible that, had we used lower levels of vitamin D in the preventive test, a difference in effectiveness of the three agents might have been manifest.

The results of this study emphasize the importance of carrying out curative tests in determining the relative effectiveness, unit for unit, of antirachitic agents. If this investigation had been restricted to a study of the comparative preventive value of cod liver oil, viosterol, and percomorph liver oil, we would have concluded that, from the standpoint of rat unitage, these antirachitics are of equal effectiveness in infantile rickets.

SUMMARY

In order to determine the relative effectiveness of cod liver oil, viosterol and percomorph liver oil, unit for unit, 365 infants were given 135, 435, or 870 U.S.P. xi units daily of one of these antirachitic agents throughout the winter months. At the end of the winter the incidence of rickets among these infants was determined by roentgenologic examination of the wrists.

The results of the prophylactic study did not indicate any significant difference in the effectiveness of these agents at the levels of units employed in this investigation. The degree of protection afforded by these antirachitics was extremely high, and only three infants among 146 receiving the lower unitage, 135 units daily, developed roentgenologic evidences of rickets.

A comparison of the curative response to cod liver oil, viosterol, percomorph liver oil and irradiated cholesterol was made on fourteen rachitic infants. These tests revealed that the daily administration of 435 units of cod liver oil, percomorph liver oil, and irradiated cholesterol brought about good healing in two, four, and three rachitic infants, respectively, whereas the same number of units of viosterol failed to bring about satisfactory healing in two rachitic infants. The results of the curative study, therefore, would seem to indicate that, rat unit for rat unit, vitamin D of animal source (cod liver oil, percomorph liver oil, and irradiated cholesterol) is more effective in the treatment of infantile rickets than is vitamin D of plant origin (viosterol).

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1 WEST SEVENTY-THIRD STREET

TETANY IN THE NEWBORN

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THREE cases of tetany in the newborn and a fourth suggestive case were reported from this clinic previously. Subsequently we have observed seven cases. The reports of these are given below.

CASE 1.—A premature baby, one hour old, weighing 4 pounds 4 ounces, was admitted for care in the nursery. He was delivered at home following an easy labor. He was fed breast milk and grew well; at one month of age he began to twitch. The blood serum calcium taken then was 5.4 mg. per 100 c.c. Ten cubic centimeters of a 10 per cent solution of calcium gluconate was given intramuscularly. Fifteen grains of calcium chloride was given by mouth five times daily, and 10 minims of viosterol was given three times daily. The baby made an uneventful recovery.

CASE 2.—A female baby twenty-four hours old, weighing 6 pounds 12 ounces, was sent to the hospital with the father who was told at the maternity hospital that the baby had a birth injury. There was a large cephalhematoma present, otherwise examination revealed nothing except that the baby was blue and twitching. Blood serum calcium was taken, and the baby died shortly after. The serum calcium was 3.9 mg. per 100 c.c.

CASE 3.—A female baby aged three days, weighing 6 pounds 12 ounces, was admitted because of convulsions and cyanosis. Labor was normal. Physical examination revealed a slightly cyanosed, normal baby. Blood serum calcium estimation showed 7.7 mg. per 100 c.c. The baby was given 10 c.c. of a 10 per cent solution of calcium gluconate intramuscularly, followed later by 20 minims of viosterol and 50 grains of calcium chloride by mouth daily. The child twitched a few times the day of admission but has been well since.

CASE 4.—A female baby, six days old, weighing 6 pounds, was admitted because of irritability, and not taking food, cyanosis and twitching of the muscles since the second day of life. The labor was difficult. Twitching of extremities and nystagmus with occasional attacks of rigidity were noted. Blood serum calcium was 7.2 mg. per 100 c.c. of blood. The child was given 10 c.c. of a 10 per cent solution of calcium gluconate intramuscularly; calcium chloride, 45 grains; and viosterol, 10 minims daily by mouth. The baby recovered rapidly.

CASE 5.—A female aged two weeks, weighing 6 pounds, was admitted because of a digestive upset of 4 days' duration and convulsions for one day's duration. The labor was normal. The baby was breast fed for four days and then put on cow's milk. Later the feeding was changed to condensed milk for 4 days, which feeding the baby vomited. Physical examination revealed that the baby's face and extremities were twitching, but she was otherwise normal. Blood serum calcium was 6.8 mg. per 100 c.c. of serum. Ten cubic centimeters of 10 per cent calcium gluconate was given intramuscularly and 50 grains of calcium chloride, and 30 minims of viosterol daily, were given orally. There were no further convulsions, and the child made an uneventful recovery.

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CASE 6.—A three-week-old male child, weighing 7 pounds, was admitted because of projectile vomiting, constipation, and loss of weight. Labor was normal. Physical examination revealed peristaltic waves and a pyloric tumor. After admission the baby had several spells of cyanosis and twitching. Blood was taken for calcium and chloride estimations. The serum chloride was equivalent to 81 c.c. of N/10 per 100 c.c.; the serum calcium was 7.6 mg. The infant was given 5 per cent glucose in normal saline by intravenous drip method for three days, receiving 2,720 c.c. At the same time, 40 c.c. of a 10 per cent calcium gluconate solution was given by the same method. The blood calcium was then 11 mg. per 100 c.c. and the chloride 92 c.c. N/10 per 100 c.c. Operation for pyloric stenosis was performed. The child made an uneventful recovery.

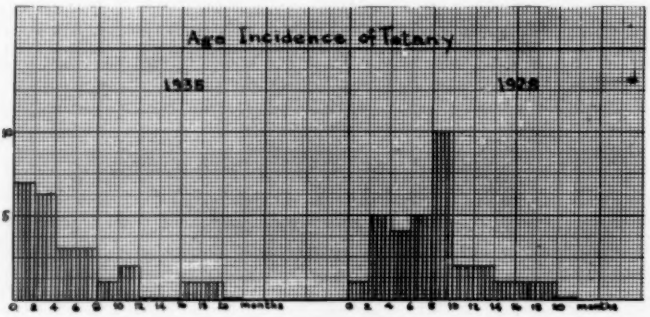

Chart 1.

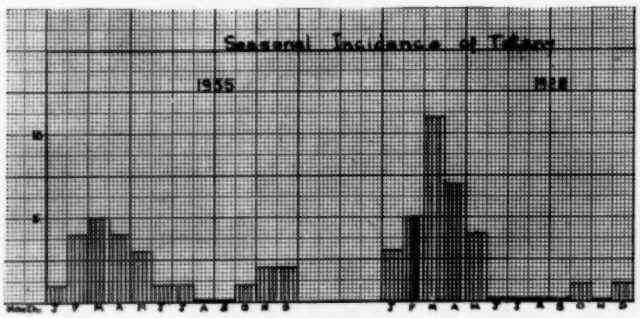

Chart 2.

CASE 7.—A male child, aged seven weeks, was admitted because of convulsions and a cold lasting two weeks and a rash lasting four days. The labor was prolonged. No vitamin D was administered. The convulsions started sixteen days prior to admission. The baby had a seborrhea of the scalp, and except for twitching of the face nothing otherwise was noted. Blood serum calcium was 6.8 mg. per 100 c.c., and blood serum phosphorus was 4.7 mg. The child was given 10 c.c. of calcium gluconate intramuscularly, followed by 30 grains of calcium chloride and 10 minims of viosterol daily. He made an uneventful recovery.

The mother's blood was examined and revealed a serum calcium of 8.4. Her diet contained no additional vitamin D but was otherwise complete.

The symptoms common to these cases are twitching, spells of cyanosis, and convulsions. In none was a crow observed or Chvostek's or Trousseau's sign seen. Tetany is a not uncommon cause of cyanosis in the newborn.

Some of these cases seem out of the newborn period, but the symptoms commenced sufficiently early to make one feel that it was not due to postnatal dietary deficiency.

In the treatment, calcium gluconate injected intramuscularly with calcium chloride and viosterol by mouth proved effectual.

This condition of tetany in the younger age groups has only recently been emphasized. A survey of the cases of tetany in the years 1928 and 1935 in the Hospital for Sick Children illustrates this point. By consulting Chart 1, one observes that previously the peak of the age incidence was from four to ten months, with most in the ten-month period. In 1935 the incidence decreases from birth with advancing age.

A similar comparison was made of the seasonal incidence (Chart 2). In 1928, 30 of 32 cases occurred between January 1 and May 1. In 1935, though there was some increase between February and May, with the exception of August and September, there were one or two cases every month.

PLACENTAL FLUID IN MEASLES PROPHYLAXIS

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A FRESHLY expelled human placenta when cut up and squeezed in a simple hand press yields a cloudy sanguineous fluid. If the fluid, together with the blood which is expelled with the placenta, is centrifuged, a supernatant fluid is obtained, the diphtheria antitoxic titer of which, in most instances, is identical with the diphtheria antitoxic titer of the serum obtained from the blood of the corresponding woman during the last stage of labor.[1] Comparison of the antitoxic titer of the placental fluid and corresponding maternal blood serum was made in 18 instances, and, as noted in Table I, the figures were identical in 13 of the 18 instances and very similar in the remaining 5.

TABLE I

COMPARISON OF THE DIPTHERIA ANTITOXIC TITERS

	PLACENTAL FLUID	CORRESPONDING MATERNAL BLOOD SERUM
	Units/c.c.	
1	0.05	0.05
2	0.03	0.03
3	0.05	0.05
4	0.20	0.20
5	0.06	0.06
6	0.14	0.16
7	0.00	0.00
8	0.00	0.00
9	0.00	0.00
10	0.00	less than 0.02
11	0.02	0.02
12	0.02	0.02
13	0.06	0.07
14	0.06	0.07
15	0.03	0.03
16	0.06	0.06
17	0.08	0.10
18	0.11	0.11

It may be noted that the titer corresponded exactly in 13 of the 18 comparisons and that the discrepancy in the other 5 was so slight as to be considered of little significance except that in these 5 the maternal serum was regularly the one which had the greater titer.

The evidence that the diphtheria antitoxic titer in placental fluid and the corresponding blood serum are similar suggested the possibility that other antibodies, for example measles, are also distributed in the same titer in the placental fluid and in maternal serum. It was not feasible to bleed women in labor to obtain sufficient amount of blood serum to

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compare its measles prophylaxis with that of its corresponding placental fluid. We, therefore, resorted to the comparison of immune adult blood serum with placental fluid in equal doses. We believe that this is justifiable, since there is no convincing evidence in the literature that there is any difference in the measles prophylactic value of the blood serum obtained from gravid women as compared to other immune adults. We were careful to obtain placentas from women whose histories of having had measles were definite.

Three preparations of the fluid, each of a pool of from four to six placentas, were made and 64 children susceptible to, and intimately exposed to, measles were injected with one of the preparations between two and five days after the initial exposure. The dosage was calculated as the equivalent of the indicated dosage of immune adult serum. Thus for complete protection of a child up to three years of age exposed no longer than five days from 12 to 15 c.c. is indicated and 4 or 5 c.c. for each additional year varying directly with the size of the child, with the maximum dosage of 40 c.c. for older children, and 50 c.c. for adults. For the development of modified measles from one-half to two-thirds of the above doses should be given before the sixth day of exposure or the entire dose from sixth to the eighth day. With preparation *A*, a uniform dose of 10 c.c. was injected into the first 20 patients; 10 to 15 c.c. or 20 c.c. were the dosages used in most of the other patients. We shall therefore compare the results obtained in all cases with either of the three preparations with the results expected had immune adult serum been injected in equal amounts.

PREPARATION OF FLUID

A. Four placentas collected with the expelled blood were cut into several small pieces and squeezed in a simple fruit press. The fluid was centrifuged and the supernatant fluid was treated with merthiolate to make a 1/7,500 solution. This solution was permitted to stand for several days; when it was dialyzed to remove some of the salts. By changing the pH of this fluid to 5.4 with normal acetic acid, a heavy precipitate of hematin and acid proteins was brought down. This was centrifuged for fifteen minutes; the supernatant fluid was poured off and brought to a pH of 6.8 by the addition of normal sodium hydroxide. The fluid was then filtered through paper pulp and finally through an N-Berkefeld filter. The resulting clear amber-colored fluid was tested for sterility, bottled in 10 c.c. doses and stored in a refrigerator until used.

B and *C*. The fluid obtained from nine placentas, 1,270 c.c., was divided into two portions, *B*, 600 c.c., and *C*, 670 c.c. *B* was prepared by the same method as described for *A*. *C* differed in preparation from *A* and *B* in that the acid protein and hematin were not removed prior to filtration. This was done to compare the reactions resulting from *B* and *C*.

Merthiolate was added to the 670 c.c. to make a 1/7,500 solution and phenol 0.25 per cent. This solution was filtered through paper pulp and an N-Berkefeld; 375 c.c. was recovered. Preparations *B* and *C* were bottled in 10 c.c. doses and were refrigerated until used.

RESULTS

The results individually and collectively, as shown in Table II, were

TABLE II

PREPARATION	CASES NO.	EXPOSURE DAYS	DOSAGE C.C.	RESULTS OBTAINED		RESULTS EXPECTED
A	33	2-5	10-20 c.c.	15	M*	18
				15	P†	11
				3	F‡	4
B	17	2-5	10-20 c.c.	8	M	14
				6	P	2
				3	F	1
C	14	2-5	10-20 c.c.	8	M	9
				5	P	4
				1	F	1
Total	64			31	M	41
				26	P	17
				7	F	6

*M, modified.
†P, protected.
‡F, failed.

NOTE.—Since the 6 failures obtained were expected, good results were obtained in 57 of the remaining 58 cases and only one more failure occurred than might have been anticipated.

that fluids *A*, *B*, and *C* were effective in measles prophylaxis in doses equal to those of immune adult serum indicated. As is commonly true in the use of other measles prophylactic substances, our results indicate more complete protection than we had hoped for. Perhaps one explanation for this fact is that many of the patients were from hygienic homes where contact with measles, though definite, was not as intimate for as long a time as might have been true in less hygienic homes.

COMPLICATIONS

One child developed otitis media. One had a convulsive seizure just before onset of fever. Cough was ameliorated in most of the modified cases, but no roentgenographic studies were made. It is, therefore, diffi-

HOSPITAL EXPOSURE

CASES	EXPOSURE	DOSE	RESULTS
8	3 days	15-20 c.c.	7 remained well 1 modified measles

AFTER REEXPOSURE TO MODIFIED MEASLES

7	3 days	10 c.c.	7 protected

NOTE.—Even with dosages which were inadequate to protect half of the children definitely exposed to measles in their homes, 7 out of the 8 remained protected in the hospital, and after reexposure all 7 remained well.

cult to know how frequently pneumonia occurred. No case of frank pneumonia persisting after the measles subsided was noted. We believe that complications were markedly reduced by the use of the placental fluid.

We question the exposure in such an experiment and report it here only to point out once more[2] the futility of hospital exposures in the study of measles prophylaxis.

REACTIONS

Reactions of one kind or another were experienced by approximately two-thirds of the cases treated. Local pain varying from momentary discomfort to severe agonizing pain lasting from one-half hour to twenty-four hours and requiring sedation was experienced. In few instances, in addition to the pain, there was local heat and redness at the site of injection and in few cases general reactions, such as transitory pallor, nausea, and fever up to 101° F. The fever lasted as long as twenty-four hours. One child had an attack of asthma one hour after the injection. The attack was brief lasting less than an hour. Local urticaria was noted in two instances. There seemed to be no striking difference in the reactions between fluids *A*, *B*, and *C*. Removal of the hematin and acid protein was therefore of questionable value. Aging of the fluid for five or six months resulted in less reaction without any demonstrable loss in prophylactic value.

DISCUSSION

All of our sixty-four patients were treated at home where they were definitely exposed to measles. Casual contacts, such as those acquired while playing out of doors, in buses or classrooms were not accepted for this study. We did, however, inject eight children in a hospital ward presumably exposed to measles for three days. It is noteworthy that in the case of this ward outbreak of measles the eight presumably exposed children, all of whom were bedridden, were injected with modifying doses of placental fluids *B* and *C*. Yet only the child who was in the bed next to the child ill with measles contracted modified measles. The remaining seven escaped it altogether. Since the passive immunity to measles may not last over two weeks, these seven children were reinjected, each with 10 c.c. of the fluid *B* or *C*, quantities ordinarily inadequate to give the necessary complete protection, but all remained well. Incidentally this gave us an excellent opportunity to study at close range the reactions to the serum. In general, they were mild. The results obtained in this small group once more corroborate our observations reported several years ago with Schick[2] and since confirmed by Levitas,[3] Laning and Horan,[4] Robinson and McKhann,[5] and McGavran[6] that hospital exposures are not adequate for the study of the value of a measles prophylactic substance.

Von Groer and Kassowitz,[7] and Kuttner and Ratner[8] have shown that maternal and fetal blood have similar diphtheria antitoxic titers. Placental fluid, which we believe to be a mixture of maternal and fetal blood and interstitial fluid, has been shown by us to have the same diphtheria antitoxic titer as that of maternal blood serum and, therefore, may be regarded as having the same titer as does fetal blood serum. Placental interstitial fluid must by the same reasoning, also have the same diphtheria antitoxic titer as does either maternal or fetal blood serum.

The studies here reported indicate that the same must be true of measles antibodies and suggest the possibility that both diphtheria antitoxin and measles antibodies are transferred from the maternal circulation to the placenta and fetus. This might not necessarily be so if one condition existed, namely, if a constant interchange of immune bodies occurred between fetal and maternal circulation. Additional evidence in favor of the passive nature of the antibodies in the newborn is the relatively short period during which the infant remains immune to measles or diphtheria. Were the immunity active, one might expect it to be of longer duration. Thus we develop permanent immunity from a mild attack of measles, and with rare exception lasting immunity followed the modified type of measles, which may be so mild as to be difficult of recognition. These studies, we believe, help to clarify the question of the source of the antibodies of the placental globulin extract of McKhann and Chu.[9]

CONCLUSIONS

1. That placental fluid has the same diphtheria antitoxic titer as the corresponding maternal blood serum obtained from the general circulation during the last stage of labor is corroborated.

2. Placental fluid has the same measles prophylactic value as that of equal quantities of immune adult serum.

3. We believe that our results justify the deduction that placental fluid obtained from women immune to measles is equal to, and interchangeable with, immune adult serum in measles prophylaxis.

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PLACENTAL IMMUNITY

A Method of Determining Dosage of Placental Globulin in Measles Prophylaxis

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IN A preliminary report[1] we demonstrated a method of measuring the dosage of the whole placental globulin extract for measles prophylaxis. It was based on the finding of volume equivalents of the placental extract and maternal blood serum in terms of diphtheria antitoxin (D.A.). Thus, if 10 c.c. of the maternal blood serum contains 1 unit of diphtheria antitoxin, the amount of the corresponding placental globulin extract which contained 1 unit of diphtheria antitoxin would be the equivalent of the 10 c.c. of that blood serum. With this information plus the indicated doses of adult blood serum in measles prophylaxis known,[2] the dosage of a specific placental globulin extract could easily be determined for any child susceptible to, and exposed to, measles. We believe that we may assume that blood serum obtained during labor is no different in its measles prophylactic value than blood serum obtained from other adults immune to measles. Problem: A child aged eight years is exposed to measles for four days. The dosage of adult serum necessary for protection is between 32 and 40 c.c., or approximately 35 c.c. What is the necessary dose of placental extract? If in the case of this placental globulin extract ("B") 1 c.c. contains 0.10 units of diphtheria antitoxin and the corresponding immune serum ("A") contains 0.30 units per cubic centimeter, we would calculate the dosage of the placental globulin extract as follows: (x is the dosage sought.)

$$B/A \times 35 = x, \text{ or } 0.10/0.30 \times 35 = 35/3 = x = 11.66 \text{ c.c.}$$

If the indicated dose of adult serum is 20 c.c., the formula would be changed only by substituting 20 for 35; the indicated dosage in that case would be 20/3 or 6.66 c.c.

A common misunderstanding of the preliminary report was that we had assumed a parallel between the diphtheria antitoxin and the measles antibody in the placental extract. We desire, therefore, to emphasize that we are not assuming that diphtheria antitoxin and measles antibodies occur in parallel amounts in placental extract. Thus we have examined blood serums of women who never had measles, but both their blood serum and their placental globulin extracts contained fairly high D.A. titers. It must be true, however, that, if all of the antibodies are

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removed by extracting all of the globulin, all of the placental measles antibodies as well as the placental diphtheria antitoxin must be in this globulin extract. If, therefore, in a given case 10 c.c. of the maternal serum contains the same amount of diphtheria antitoxin as does 10 c.c. of the whole placental globulin extract, then these equivalents must also hold true for all other antibodies completely removed with the globulin. Specifically, therefore, in the case of the measles antibodies 10 c.c. of this maternal serum must be quantitatively equal to 10 c.c. of the corresponding placental globulin extract.

In the preliminary report we cited our experience with sixty cases of measles prophylaxis treated with 10 different placental extracts. The results justified our continuation of the work since they indicated that the method for calculating dosages was correct as described. The present report deals with the results obtained with sixteen different placental preparations. Ten were whole globulin extracts of placenta; three were extracts of placental tissue after the fluid had been discarded; and three were just placental fluid. These products were injected prophylactically against measles in 174 susceptible children, 166 exposed in their own homes to siblings ill with measles, and eight presumably exposed in a hospital ward. Seven of the eight were reinjected after two weeks because of possible reexposure. Thus 181 injections were given.

TABLE I

COMPARISON OF THE RESULTS OBTAINED AND THE EXPECTED RESULTS WITH PLACENTAL GLOBULIN EXTRACT OR PLACENTAL FLUID IN MEASLES PROPHYLAXIS

NO.	DOSAGE	CASES	RESULTS			EXPECTED RESULTS		
			PROTECTED	MODIFIED	FAILED	PROTECTED	MODIFIED	FAILED
2	10.0 c.c. G*	5	3	2	0	4	1	0
3	15.0 c.c. G	5	2	2	1	1	3	1
4	13.3 c.c. G	4	1	1	2	0	2	2
5	20.0 c.c. G	4	1	2	1	0	2	2
6	10.0 c.c. G	7	2	3	2	1	5	1
7	5.7 c.c. G	12	2	7	3	3	8	1
8	6.6 c.c. G	10	5	4	1	3	7	0
9	8.3 c.c. G	5	1	2	2	1	3	1
10	3.3 c.c. G	12	5	5	2	5	6	1
11	4.0 c.c. G	15	6	8	1	6	9	0
15	10.0 c.c. T†	6	3	3	0	3	3	0
16	4.2 c.c. T	10	4	6	0	5	5	0
17	5.6 c.c. T	7	0	6	1	1	6	0
A	10-20 c.c. F‡	33	15	15	3	11	18	4
B, *C*	10-20 c.c. F	31	11	16	4	6	23	2
	Total	166	61	82	23	50	101	15
Results			37%	49.4%	14%	30%	61%	9%
Expected results			30%	61.0%	9%			

*G indicates whole globulin extract of placenta.

†T indicates whole globulin extract of placenta after the free fluid has been expressed.

‡F indicates the free fluid expressed from the placenta.

NOTE: In numbers 2 to 17 inclusive the dosage is equivalent to 10 c.c. of immune adult serum. In *A*, *B*, and *C* the dosages were calculated equal to 10-20 c.c. of adult serum.

The volume equivalents between the immune maternal serum and the corresponding placental product was determined as previously described. The first thirteen products were used in quantities equal to 10 c.c. of adult serum, whereas with the placental fluids the doses varied between 10 and 20 c.c. The results were judged according to the expectations in each case had immune adult serum been used in equivalent dosage.

Table I indicates how close our results were to the expected results. As usual, the number of complete protections was higher than was expected. This is the common experience with all effective products used in measles prophylaxis, and we believe can be explained in part on the fact that some of the children treated came from hygienic homes where the contact with measles was brief, and in some instances, as in case of the hospital ward, where contact casual or through a third person.[3] Under such conditions a higher per cent escape the disease. One hundred and forty-six of the 166 patients treated at home were moderately or intimately exposed to measles of their siblings, whereas 20 were casually exposed. For example, a child of ten months might have been exposed to the measles of his sick brother, but there might be some question as to the certainty of this exposure since babies of that age are usually carefully shielded. In others of these 20 cases the illness of their siblings was discovered early in the prodromal stage. These children were immediately separated from the sick contacts. The exposure was probably definite in these instances, but its duration must have been brief. In this group we expected 5 protections, 13 modifications, and 2 failures. Instead, we obtained 16 protections, 2 modifications, and 2 failures. If the results are corrected by subtracting this group of 20 cases, the comparison between results obtained and expected results are as given in Table II.

TABLE II

RESULTS AFTER ELIMINATING THE 20 CASES OF CASUAL EXPOSURE

	CASES	PROTECTED	MODIFIED	FAILED
Results	146	31%	55%	14%
Expected results	146	30%	61%	9%
Hospital results	8	7	1	0
After reinjection	7	7	0	0

Table II shows a much closer comparison of the results obtained with the expected results when only definite and intimate exposures are considered. The results indicate that the method of measuring the dosage of the whole globulin extract of the human placenta is reliable and may be recommended for use.

DISCUSSION

The more recent work with placental globulins in measles prophylaxis has been done with fractions of the whole globulin extract with which the present paper deals. Since, in a process of fractionation of the whole

globulin extract some of the antibodies are lost with the fractions not used, it is not possible to apply our method for direct determination of the dosages of the more refined placental products or those globulin fractions more recently by McKhann and his coworkers,[4] or of those manufactured commercially. It can, however, be of some aid in this direction as will be shown later.

We have shown that the fluid expressed from the placenta has the same D.A. titer as does the maternal blood serum, and in the preceding paper we have demonstrated that this placental fluid is effective in measles prophylaxis in the same dosage indicated for adult blood serum. This information obviates the need for maternal blood serum to compare with the placental globulin. Instead, the placental fluid may be compared with the globulin extract of the placenta in order to get the equivalent necessary for determination of dosage in measles prophylaxis.

We believe that placental immunity is most likely humoral. Extracting the placental globulins, therefore, yields those antibodies contained in the placental fluid, for example, just as extracting the liver or spleen globulins would probably yield the antibodies contained in the hepatic or splenic fluid. We have shown that placental fluid and maternal blood serum have similar D.A. titers and similar measles prophylactic value. This makes it possible to illustrate more easily our method of measuring the dosage of placental globulin extract. Thus, if a serum contained x units of diphtheria antitoxin and y measles antibodies per 100 c.c., then 100 c.c. of the corresponding placental fluid must contain x units of diphtheria antitoxin and y measles antibody. If, by extraction of the placental fluid globulins we obtain 20 c.c. of the extract, this 20 c.c. must still contain x units of diphtheria antitoxin and y measles antibodies, disregarding the slight loss incurred in extraction. We have, therefore, merely concentrated the antibodies five times. Applying the original formula in a case which requires 40 c.c. of adult blood serum, we would give $B/A \times 40$ or $20/100 \times 40$ or 8 c.c. of placental globulin extract.

We have treated forty children for measles prophylaxis with commercial placental globulin extracts, adhering to the dosages recommended, except that we increased the dosage in some instances. The preparations were effective but not adequate, since a large percentage of children (41 per cent) failed to show the expected amelioration of measles. These products were made to contain a certain per cent of nitrogen and were made of pools of 500 to 1,000 placentas. By increasing the nitrogen content, better results should be obtained. It also seems reasonable to expect a product of uniform effect if each preparation is made of so large a number of placentas. Perhaps one suggestion might be derived from our studies, which would help in arriving at a dosage of the commercial product, that is, to find out the adult blood serum equivalent of the pooled placentas by measuring the D.A. titers of the placental fluid squeezed from the entire batch of placentas and

that of the complete globulin extract of the placentas and fluid combined, and by applying these figures to the formula, $B/A \times$ volume of whole globulin extract = adult serum. B is the D.A. titer of 1 c.c. of the globulin extract and A the D.A. titer of 1 c.c. placental fluid. At least the measles prophylactic value of the original extract would be known if this were done.

REACTION

The whole placental globulin extract causes reactions in about two-thirds of the cases. These are usually transitory local pain at the site of the injection. Occasionally, however, they are more severe and are accompanied by fever, usually not over 101° F. Aging the extract for six months seems to reduce the severity of the reactions to it. Three preparations (15, 16, and 17) were made from placental tissue after the fluid had been expressed and discarded. These preparations were paler than those prepared from the placenta plus fluid. The twenty children who were injected with these three extracts suffered only slight local pain, or had no reaction at all. This observation bears further study. If corroborated, it offers a placental preparation which can be concentrated, the dosage of which can be determined, and to which the reactions were very slight.

CONCLUSION

A method is described for measuring the dosage of the whole globulin extract of human placenta for measles prophylaxis. One hundred and eighty-one injections in 174 children yielded results which were very close to our expectations, thus indicating the validity of this method.

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MULTIPLE NEURITIS FROM DIPHTHERIA TOXOID

Report of a Case

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THE possible untoward reactions which may follow common immunologic procedures are hazards that must not be disregarded because of their rarity. At the same time the infrequency of such complications makes their record valuable from both a diagnostic and a prognostic viewpoint. Accordingly, the following instance of generalized paralysis resulting from the use of alum-precipitated diphtheria toxoid is reported.

CASE REPORT

Baby M. G., female, aged one year, two days, was given the standard 0.5 c.c. dose of proprietary brand of alum-precipitated diphtheria toxoid subcutaneously on March 26, 1934.

The infant had been under care for regulation of feedings since the age of three weeks. Her birth, development, and past course had been uneventful. One sibling, aged six years, and both parents were healthy. There were no known instances of allergic manifestations or sensitization in the family.

Approximately two and one-half weeks before immunization the patient had a very mild attack of measles, contracted from her sister. Preliminary use of parent blood unquestionably modified this illness. At the time of immunization the mother remarked that the child appeared to have a slight head cold, but there was no evidence of this infection in her nose and throat, and her temperature was normal. Other than the present illness there was no reaction, local or systemic, following immunization.

During the next week the parents noticed a gradually developing weakness and lessening of physical activity in the child. Previously she had just started walking, but the disability progressed until the child was finally confined to her bed. Except for the lassitude and weakness she was thought to have been well since she had remained cheerful and played with her toys as usual. Her appetite was good; fever was never noted; and there was no evidence of any pain or discomfort. Finally she was unable to sit up or even raise her head from the bed.

The patient was examined first on April 17, three weeks after receiving the toxoid. At this time she was bedfast, and active motion of her arms, legs, and body was practically absent. When raised to a sitting position, her lower jaw dropped sharply, and she was unable to balance or support her head. All of the voluntary muscles appeared equally hypotonic and paretic. The deep and abdominal reflexes were absent. Mentally the child was alert and attentive. Although she resented examination, no definite evidence of deep tenderness nor surface hyperesthesia was elicited. The extraocular movements and pupillary reflexes were normal. Speech and swallowing were unaffected. The gag reflex was active, and her breathing was normal. There was no nuchal rigidity, and Kernig's sign was negative. Pulse, temperature, and further findings on physical examination were normal save for a small indurated mass at the site of the previous toxoid injection. On consultation the suggestion of excising this nodule was raised and the following morning the lump

was removed en masse as a possible persistent focus of toxic material. Massage and passive motion were advised and strychnine in moderate dosage was given by mouth.

For a period of twelve days, from April 17 to 29, the patient's condition was unchanged. After that a slow but progressive improvement was noted. Finally, by May 9, forty-four days after receiving the toxoid and approximately three weeks after the maximum paralysis, the patient was able to raise her head from the bed and to maintain herself in a sitting position by use of her arms. All reflexes were still absent. Two weeks later, on May 23, the patient was pushing herself around in a "walker" and could get into a sitting position from her back although she was unable to raise herself from a prone posture. The abdominal reflexes were now quite active, and faint responses were obtained in the arms, but the knee and ankle jerks were still missing. By June 12 the child was able to pull herself up and stand with support. Finally on June 20, approximately twelve weeks after the onset of illness, all reflexes were normally active and muscular strength was returning rapidly although she did not try to stand alone. Subsequently she relearned to walk and later development was uneventful.

DISCUSSION

The transient paralysis of this infant is typical of a multiple neuritis involving the peripheral motor nerves. The causal relationship between the diphtheria toxoid and multiple neuritis in this patient may be best substantiated by considering briefly the possible etiology of neuritis of this type. The following factors merit consideration in the present case.

1. *Defective Toxoid.*—The possibility that the observed paralysis resulted from the use of unmodified or contaminated toxoid is excluded inasmuch as the patient's dose was part of a ten-dose package. The remainder was given uneventfully to other children, in part before and in part after the fraction in question.

2. *Diphtheritic Infection.*—The question of active diphtheritic infection at the time of immunization, suggested possibly by the recorded history of a "cold," was contradicted by the objectively normal nasopharynx, normal temperature, and absence of evident illness at the moment or later. Likewise the most common sites of postdiphtheritic paralysis, the palate and eyes, were not involved in the patient. Equally noteworthy is the fact that complete paralysis of the extremities was fully developed within a period of three weeks from the time of toxoid injection. Postdiphtheritic paralyses of the extremities on the other hand have been quite uniformly observed only after a latent interval of from five to eight weeks after infection.

3. *Neuritis Complicating Measles.*—The possibility that paralysis in this child complicated the antecedent measles is quite improbable inasmuch as the commonly recorded neurologic complications of measles are encephalitic in nature. Even more significant is the fact that nervous complications of measles are uniformly noted coincident with, or follow immediately after, the eruptive stage of the disease.

Thus Ford,[1] in a review of the neurologic complications of measles, lists only two cases (Coote, Boenheim) with paralysis suggestive of

polyneuritis. Paralysis in these two cases was noted first on the third and fifth days, respectively, after the onset of the measles. The balance of the paralytic complications involved patients with acute ascending type of disease, frequently associated with sphincter involvement and often showing residual spasticity, indicative of actual myelitis. Ford concluded that "polyneuritis is rarely, if ever, a true complication of measles."

Subsequently Blackfan[2] has described four personally observed cases of peripheral neuritis complicating measles. He writes that the paralysis appeared "four or five days after the disappearance of the eruption" and that "it is possible that these neurologic disturbances are manifestations of a form of encephalitis" which "develops several days after the disappearance of the eruption and is characterized by a reappearance of fever with neurologic signs of varied character." Thus it is apparent that the illness of the present patient can be associated with measles only by interpreting her disease as an original and unique type of neurologic complication in this disease.

4. *Paralysis After Immunologic Therapy.*—A syndrome of peripheral nerve paralyses sporadically complicating the use of therapeutic and prophylactic serums and vaccines has been observed repeatedly. The nature of this illness, as reported in the literature, agrees with the clinical course of the present patient as closely as the previous explanations vary from the observed picture. While these neurologic complications of ordinarily innocuous therapeutic procedures have been commonly viewed as a type of anaphylactic phenomenon because they are often associated with manifestations of serum disease,[3] Young,[4] in a review of fifty cases, noted that 25 per cent occurred without urticaria or evidences of serum reaction. The hypothetical pathologic basis of allergic cases is a perineural edema; in the absence of allergic features a direct toxic action on the ganglion cells or their processes is predicated. The latent period between administration of the serum or vaccine and onset of paralysis has been uniformly noted to vary from three to ten days. On a limited number of cases, Gordon[5] has suggested that paralyses of prophylactic and therapeutic dosages might be differentiated by a variation in the time of onset and duration of illness. The extent of the neuritis may vary from single nerve involvement to a typical multiple neuritis. Although the outcome of the disease ranges from permanent paralysis to a complete recovery (noted in 40 per cent of Young's group) it is interesting to find that three of the four patients with multiple neuritis in this author's series recovered completely. Including the present case, the recovery rate is 80 per cent for the type with generalized paralysis. Whether this implies a disseminated and therefore diluted intoxication in contrast to the localized paralyses with a lower recovery rate is an interesting speculation. Prognostically the first reported sign of a permanent paralysis is the appearance of muscular

atrophy. The specific immunologic agent responsible for neuritis is apparently not significant since typical cases have been observed following the use of bacterial vaccines (typhoid, staphylococcus), antiserums (diphtheria, tetanus, pneumonia), and immunizing toxins (scarlet, diphtheria in the present case). The incidence of these untoward reactions is obviously extremely low while the value of the therapeutic measures involved is so well established that complications of this kind should be recalled merely as exceptions which prove the rule when patients are reassured as to the safety of our current therapeutic procedures.

SUMMARY

A case of multiple neuritis complicating the use of alum-precipitated toxid in immunization against diphtheria is reported to illustrate a type of untoward reaction which may follow the use of various common therapeutic preparations. The present case is apparently the first to be reported following the use of diphtheria toxoid. Complete recovery from the extensive paralysis noted in this instance shows that the prognosis is more favorable than the peak of the distressing illness might indicate.

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LIPOMATOSIS IN INSULIN-INJECTED AREAS IN A DIABETIC BOY, AGED THIRTEEN AND ONE-HALF YEARS

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ALTERATIONS of the skin and subcutaneous tissues due to insulin at the site of the injections have frequently been observed. The changes first described were the immediate local reactions which were temporary in nature. They were attributed to protein sensitivity, faulty technic, poor asepsis, trauma, etc.

There have been many reports both in the American and European literature of permanent changes following insulin when identical areas are injected over a long period of time. Most of the cases described were the more familiar lipodystrophies or atrophies. According to Depisch,[1] these may occur in about 10 per cent of the patients who have been treated with insulin over a period of years. In 1926 he reported local lipodystrophies in five cases. Since then a large number of cases have been added to the literature. Gellerstedt[2] as early as 1932 was able to review forty-seven cases from the available literature.

Another type of alteration, namely, subcutaneous tumefactions, lipomalike masses, have been described more recently. One of the earliest reports appears to be that of Eeg-Olofsson[3] in 1930. He reports the case of a girl sixteen years old in whom exploratory excision showed chronic inflammatory changes and hyperplasia of the connective tissue. Clinically these tumefactions closely resembled lipomas. The first and only report we found in this country was that of Rowe and Garrison[4] in 1932. They reported an increase in the subcutaneous tissue in the outer aspect of each arm of a boy eight years old. Subsequently after an examination of fifty patients they mentioned the discovery of three more patients, twelve years, nineteen years, and fifty years old, respectively, showing these tumefactions. Apparently no biopsies were made because none was reported. Gellerstedt[2] in 1932 reported four cases in children three and one-half, five and one-half, nine and sixteen years old, respectively. Histologic examination of the tumefactions in one of these cases coming to autopsy, revealed enormous lipomatoses with old and recent inflammatory changes. Priesel[5] in 1935 reported a case of an eight-year-old diabetic boy with large tumefactions on the thighs and arms. His case also came to autopsy, and histologic findings were identical with the findings of Gellerstedt.

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Adlersberg[6] in 1935 described a case of fatty tissue hyperplasia in a girl twenty years old. Fischer (verbal communication) presented similar cases at the pediatric section of the New York Academy of Medicine.

Among our diabetic children a case was seen recently and it is reported here on account of its unique features and a possible clew to the much debated etiology of these alterations.

G. C., aged thirteen one-half years, white, male, of Irish extraction, had diabetes mellitus for four and one-half years. His diet was high in carbohydrates and

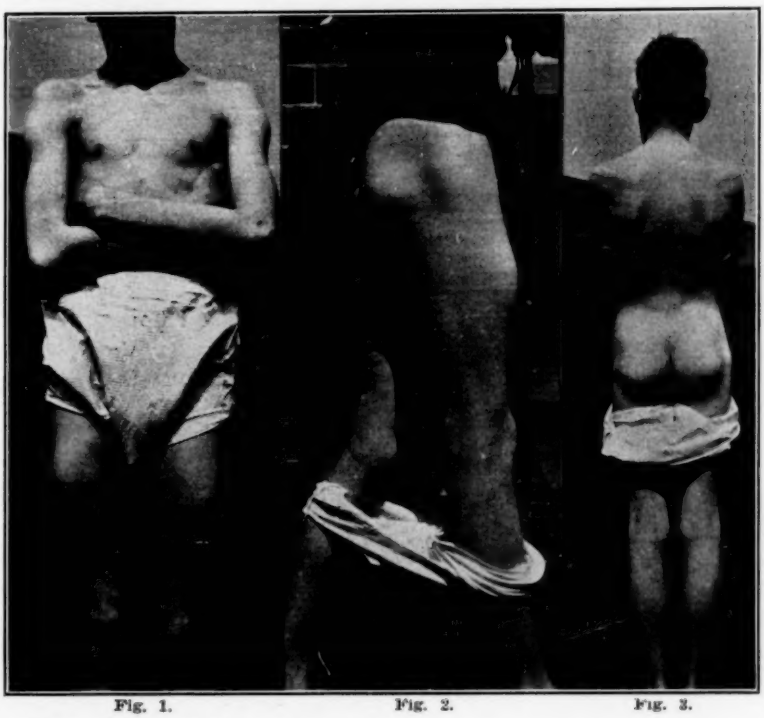

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Anterior view.
Fig. 2.—Lateral view.
Fig. 3.—Posterior view. Lipomatosis of arms and thighs due to insulin injections.

low in fat. It varied between 300 gm. of carbohydrates, 70 gm. of protein, 70 gm. of fat and 400 gm. of carbohydrates, 100 gm. of protein, 100 gm. of fat, which it is at present. The disease has been fairly well controlled with two injections of insulin daily, one before breakfast and one before supper. The insulin requirements per day have varied between 50 and 80 units during the past two years. His blood cholesterols have varied within normal limits. His progress in weight and growth has been satisfactory. Two years ago very small swellings were noted in the insulin-injected areas: both biceps, both buttocks, and the anterior aspect of both thighs. These swellings were described as localized, edematous, symmetri-

cally distributed tumefactions. In spite of our admonition to avoid these areas in the future, the patient continued to use them for insulin injections because "it hurt less" when these areas were used. The insulin appeared to be absorbed as well from these areas as elsewhere. As a result of the continuous use of these areas the swellings have increased steadily in size. In April, 1936, he showed in the same areas (Figs. 1, 2, and 3) numerous symmetrically distributed tumors, varying from the size of a hen's egg to the size of a fist. They were hemispherical in shape, raised above the skin surface, of soft consistency, lipomalike. They were freely movable, but adherent to the skin. The skin was stretched in the affected areas, but appeared of normal color. There was no pain or other subjective sensation.

Histologic Examination.—These sections show a moderate hyperkeratosis with edema of the epidermis, portions of which appear to be slightly atrophied. The

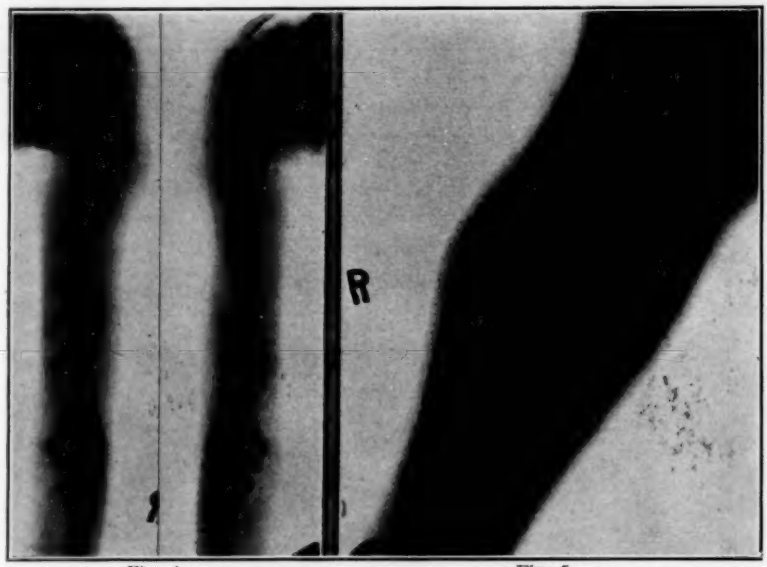

Fig. 4. Fig. 5.

Figs. 4 and 5.—X-ray pictures of arms and thigh showing distinctly the outline and extent of lipomatosis following insulin injections.

corium is somewhat edematous, the site of a slight chronic inflammatory reaction. There appears to be a moderate fibrosis of the corium. The outstanding feature, however, is the attached adipose tissue which is composed of very large cells, and shows evidence of encapsulation. Besides the other changes the adipose tissue comes fairly close to the epidermis in one place, and within it one sees a hair follicle and a smooth muscle bundle as is frequently the case when the skin atrophies. Sharlach red stain disclosed no peculiarities in the corium.

It may be pertinent to mention here the patient's technic of syringe sterilization. It has been his custom to keep his syringe and needle in an enamel dish containing rubbing alcohol. Before injecting the insulin, he would boil the syringe and needle in water for seven minutes, then he would replace them in alcohol to cool, and thereupon he would draw up the necessary amount of insulin and inject it forthwith after sterilization of the skin surface with the rubbing alcohol.

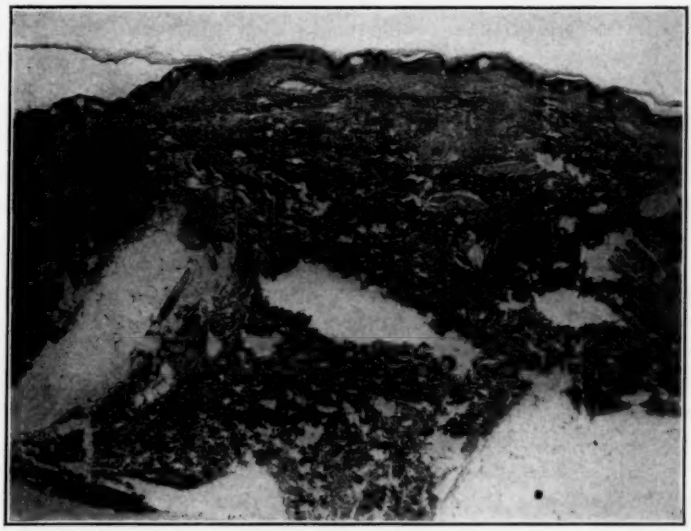

Fig. 6.—Low power magnification showing chronic inflammatory reaction and fat hyperplasia in the corium.

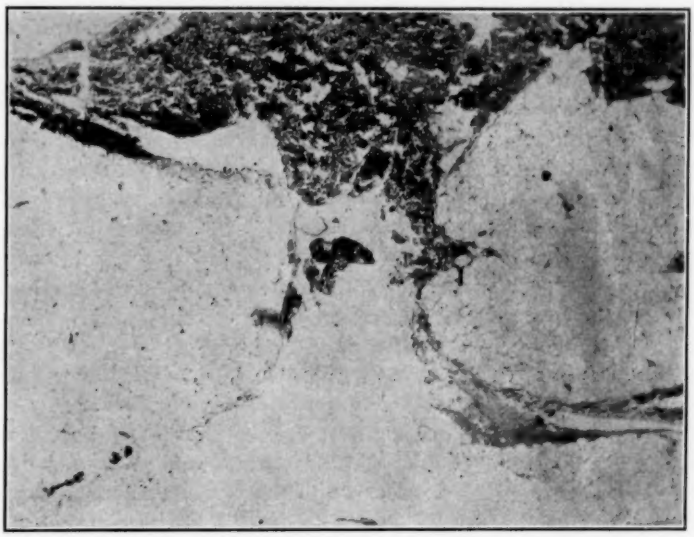

Fig. 7.—High power magnification showing chronic inflammatory reaction and fat hyperplasia in the corium.

COMMENT

It is evident that these subcutaneous tumefactions in diabetics develop gradually following insulin injections when the same areas are used over a long period of time. They have been seen to develop as early as four months and as late as several years. The clinical appearance has been similar in all the reported cases. The absence of inflammatory changes of the skin, the lipomalike, soft consistency, stretched, slightly thickened and adherent skin, and symmetrical distribution, have been emphasized by all authors. The size of these lesions has varied from that of a pigeon's egg to that of a fist or even larger. In our patient one of them on the thigh measured 8 by 14 cm. A pronounced hypalgesia of the skin in these areas, found in many of the cases, was present in our case also. This phenomenon is apparently secondary and is due to repeated traumatization of the fine sensory nerve endings. The location has been practically the same in all cases: the upper third of the arms, the anterior and lateral aspect of the thighs, and the buttocks, wherever insulin was injected.

There is sufficient proof to regard these tumefactions as local lipomatoses. The macroscopic and microscopic examination of the sections examined show that they are composed primarily of hyperplasia and hypertrophy of the subcutaneous fat tissue. A moderate amount of older and recent inflammatory reaction cannot change the view that the fat tissue hyperplasia is predominant. The increase of the connective tissue can be much easier explained than the lipomatosis. Repeated traumatization from the injection of various irritants causes inflammatory reactions which result in fibrous changes. For comparison in our case a biopsy specimen taken from an apparently normal skin area where insulin was given recently, showed a moderate inflammatory reaction in the cutis, perivascular edema, and mononuclear infiltration, without any hyperplasia of the subcutaneous fat tissue.

No serious sequela has been observed so far, and the lipomatous process seems to be benign. No therapy has influenced them, but a definite reduction in size can be noticed when further injections in the area are avoided. According to some authors, local lipodystrophy is more common then lipomatosis, yet Priesel observed lipomatosis in thirty-six of fifty-four diabetic children, whereas there were only eight instances of atrophy in his group. It appears that lipomatosis is more frequent in this country than the literature would seem to indicate. Since the discovery of our case, we have learned of similar observations by several physicians. One of us (G. B.) has recently seen nine cases in a group of ten diabetic children at a children's diabetic camp at Mountainville, N. Y. Nine of these children showed varying degrees of hypertrophy. The one child who did not show hypertrophy had had diabetes for only a few months.

All of the authors seem to agree that lipomatosis occurs primarily in children. If insulin is the cause, might it not be related to the larger doses of insulin which children require? The etiology of both types of chronic local changes in the skin (lipodystrophy and lipomatosis) is still obscure. Why lipodystrophy appears in one person, lipomatosis in another, or both in the same person (Dinkler[8]), one can only speculate. Many explanations have been offered for the pathogenesis, but the various hypotheses could not be confirmed experimentally. Some of the authors have variously attributed these alterations to the brand of insulin, to its impurities, to the preservative used (trieresol). Others have suggested a mechanical traumatic injury to the delicate protoplasmic envelope of the fat globules. Feyrter[9] associates the two conditions and proffers the possibility of a regenerative hyperplasia secondary to a primary atrophy. A most plausible explanation is given by Gellerstedt. He believes in a local physiologic assimilatory effect of the insulin in cases of lipomatosis causing a local fat retention similar to its systemic effect in individuals in whom a gain in weight is accomplished with insulin. He considers the atrophies paradoxical manifestations and feels that in those instances in which atrophic changes occur, hereditary constitutional, endocrine, and other factors play some rôle. In our case we considered the possibility that the lipomatous changes were due to the presence of alcohol and its ingredients in the insulin because of the manner in which the patient sterilized the syringe and needle before injections. In response to our inquiry as to the ingredients of the rubbing alcohol used by the patient, the manufacturers informed us that it consisted of 70 per cent alcohol plus approximately 8 per cent of acetone, 4 grains of zinc sulphocarbonate per fluid ounce, and of small quantities of tincture of quassia. It is possible that repeated injections of these products even in minute quantities for a prolonged period of time may have given rise to the changes described. The fact is that practically in all cases the injections were given by the patients themselves, or some member of the family. The method of administration and the technic of sterilization have been without any supervision. In a recent communication, however, Dr. Alexander Marble[10] of Boston states they (Joslin and others) have not been able to relate the method of sterilization of the syringe either to the atrophies or to the indurations, and the etiology of these alterations following insulin administrations remains unknown.

SUMMARY AND CONCLUSIONS

An instance of lipomatosis in the insulin-injected areas of a thirteen-and-one-half-year-old diabetic boy has been reported. The literature of this unusual condition has been reviewed, and the various sugges-

tions as to its etiology have been mentioned. Though the precise etiology of this condition remains unknown, the condition is probably more common than the literature would seem to indicate. We suggest that physicians, when they examine their diabetic patients, keep the possibility of lipomatosis in mind. As a preventive measure, frequent changes in the site of the insulin injections should be strongly advised.

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TYPHOID FEVER IN CHILDREN

A Study of 60 Cases

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THE classical signs, symptoms, and course of typhoid fever, as described by Gerhard[1] in his paper which clearly differentiated typhoid and typhus fever, have been reduplicated countless times in the wards of our adult hospitals, and are usually readily recognizable. That typical cases in children are recognized is to be acknowledged, but because of the declining frequency of the disease in this country since the advent of the Public Health and Marine Hospital Service (1902), the number of cases seen by any individual must necessarily remain small. In an adult the history is usually highly suggestive, but in children, in whom the complaints are not those of the patient, but rather those observed by a second person, the history may not include those symptoms which we have learned to accept as indicative of typhoidal infection.

For these reasons, and because the only recent reviews are in foreign journals, it was felt that a brief survey of a group of cases seen in the Children's Hospital might clarify the symptomatology and facilitate the diagnosis in subsequent cases.

The danger of allowing a case on the wards or in the home to remain unsuspected, even for a few days, is obvious. In seven of the sixty cases studied, there were other members of the family who were ill with typhoid fever, and had these primary cases been diagnosed at the onset, cross-infection might have been averted.

Because of incomplete records some of the observations are made on numbers of cases slightly less than sixty. When the nature of the immediate subject permits, tables are used to abbreviate discussion.

GENERAL CONSIDERATIONS

From one to eight cases of typhoid fever are seen each year on the wards of this hospital. The average number is 3 or 4.

Seasonal Incidence.—Figure 1 is self-explanatory, and the curve roughly parallels that for the seasonal incidence in adults, although in the instance of the cases studied, the peak comes earlier in the year. It is not then, the "autumnal fever" seen in the adult epidemics of past years.

From the Infants' and Children's Hospital, Boston, and the Department of Pediatrics, Harvard Medical School.

Sex and Age.—There is no significant difference in the occurrence in the two sexes. A consideration of the age incidence in this series is of interest, for, contrary to the accepted statement that typhoid fever in children under six years is rare, 50 per cent of the cases occurred in children under five and one-half years of age. The number of cases occurring in infants is too small to warrant separate analysis, and for statistics reference should be made to Griffith's report[2] of

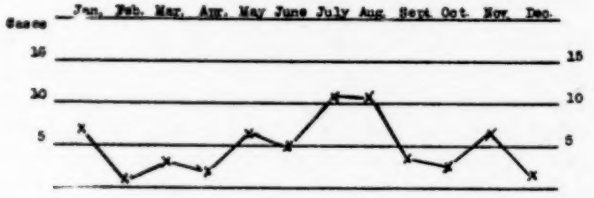

Fig. 1.

seventy-five cases in infants. The youngest infant in our series was seven months old; a considerable number of cases in younger infants have been recorded, of which Weech and Chen's[3] twenty-one-day-old child represents the youngest nonintrauterine infection.

TABLE I

AGE IN YEARS	1	2	3	4	5	6	7	8	9	10	11	12	13
No. of cases	5	3	8	4	11	6	6	4	3	6	3	0	1

Symptomatology.—With the presentation of the accompanying tabulation, which is compiled from the complaints on the entry of the patient, it must be reiterated that, for the most part, the symptoms are those noted by the parents. Obviously, if parents have been up for several nights with a thrashing, delirious child, they may fail to recall a slowly increasing apathy, a light cough, or a relatively trivial epistaxis. And it is to be added that a mother's impression of "fever-

TABLE II

SYMPTOM	NO. OF CASES		SYMPTOM	NO. OF CASES	
	PRESENT	FIRST SYMPTOM		PRESENT	FIRST SYMPTOM
Fever	50	22	Pain in, or stiff, neck	4	1
Abdominal pain	29	3	Chills	4	0
Vomiting	20	0	Blood-streaked stools	2	0
Headache	15	4	Pain in extremities	3	0
General malaise	12	8	Nausea	2	0
Drowsiness	11	1	Constipation and diarrhea	2	-
Constipation	11	0	Sore throat	1	1
Diarrhea	13	1	Vertigo	2	0
Delirium	12	0	Dyspnea	1	0
Anorexia	9	1	Tenesmus	1	0
Cough	9	1	Tarry stools	1	0
Apathy	8	3	Coma	1	0
Irritability	6	2			
Epistaxis	6	0			

-ishness" is more frequently based on listlessness, apathy, and drowsiness than on a thermometer reading. However, the figures for the incidence of such objective symptoms as vomiting, abdominal cramps, delirium, etc., are probably valid. Attention is especially called to the frequency of abdominal pain and cramps during the onset of the disease, for an incidence of this magnitude is frequently discounted.[4] The high incidence of abdominal pain is in agreement, however, with the observations of Holpern,[5] and Hand and Gitting.[6] The severity of the abdominal pain and the presence of localized tenderness secured the admission of one of our patients to surgery; when the abdomen was opened for appendectomy, the lymphoid hyperplasia suggested the true diagnosis. Except for abdominal pain, the disease in children is really characterized by the benignity of the gastrointestinal symptoms, and Vergara[7] uses this feature in distinguishing between typhoid and paratyphoid fevers.

In general there is marked variability in the nature of the first symptom to be noted, but in 40 per cent of the cases fever apparently marked the onset of the illness.

The disease in children characteristically presents a more rapidly moving and dramatic onset than is seen in adults. Symptoms referable to the central nervous system are often present and frequently prominent.

The rapidity of onset is attested to by the compilation showing the numbers of cases admitted in relation to the number of days since the appearance of the first symptom (Table III).

TABLE III

DAY OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	19	29	30
No. of cases admitted	0	0	3	2	7	7	5	6	7	8	3	0	2	4	3	1	1	1

PHYSICAL EXAMINATION

Only those signs which are of special interest in typhoid fever will be considered. *Rose spots,* though seldom abundant, were usually present at some time, but in eight cases seen during the first two weeks of illness they were never observed. Three of these cases were admitted during the first six days of illness. In nineteen cases rose spots were present during the beginning of the second week of illness. Eleven patients developed rose spots under observation; in two instances they appeared as early as the sixth day, and in every case before the fifteenth day. Because of variations in the time of admission of cases, in the numbers of rose spots present, and in the diligence of the search for them, the percentage incidence of this diagnostically valuable rash varies widely in the cases in the literature; however it can be said that from the onset to the middle of the second week, rose spots are usually found if a search is made for them.

TABLE IV

ROSE SPOTS ON ADMISSION

DAY OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	19	30
No. of cases	0	0	0	1	1	4	4	6	7	3	2	0	1	3	3	1	1

Spleen.—Although in 13 cases, which were admitted between the third and tenth days of illness, the spleen was never palpable, it is impossible to know how actively its presence was sought. In each of 6 cases the spleen was felt as early as the fifth day and, with the above exceptions, was always palpable by the end of the second week. In 8 cases in which the spleen appeared under observation, the enlargement occurred between the sixth and thirteenth days in all but one. In that case enlargement was not noted until the seventeenth day.

LABORATORY DATA

White Count.—There was marked variation in the extremes of the white count, and during the course of the disease in 58 cases total counts of 1,900 to 25,000 were observed. Similarly, and purposely restricted to those cases which showed relatively low counts, the number of polymorphonuclear leucocytes showed variations from 26 per cent to 90 per cent. Fifteen cases showed white counts of over 10,000 on admission, and in three instances repeated counts were above this level. Unfortunately for the purposes of statistical analysis, the blood studies were not repeated in 5 of these 15 cases. Most of the cases with high white counts on admission were admitted during the first week, and in the 7 cases in which a leucopenia subsequently appeared that change took place before the twelfth day of the disease. Of particular interest are 3 cases which showed, respectively:

1. W.B.C. 21,000 on the 5th day
   5,300 on the 9th day
2. W.B.C. 25,000 on the 3rd day
   6,600 on the 5th day
   4,000 on the 6th day
3. W.B.C. 13,000 on the 4th day
   2,300 on the 7th day

These last 7 cases, insignificant in number, nevertheless, suggest the possibility that there is a relatively high white count during the original period of multiplication of bacilli in, and migration through, the wall of the gastrointestinal tract and that this leucocytosis prevails until the invasion of the blood stream. Gallagher[9] has suggested that the leucopenia in typhoid fever is due to the toxic destruction of leucocytes in the circulating blood, rather than to depression of the bone marrow. His inference is based on the apparent activity of the bone marrow, as evaluated by filamentous-nonfilamentous ratios.

Blood Cultures.—In three cases previously positive, blood cultures became negative by the eighth day, and 2 cases admitted on the seventh day of the disease showed persistently negative cultures; it is not then surprising that in about 25 per cent of cases admitted during the second week positive cultures were never obtained from the blood. Lantin[10] has shown that the mortality increases with the persistence of positive blood cultures, and, while the numbers of deaths in our series are too small to warrant any addition to his figures, the fact that in every nonrecrudescing case the blood was sterile before the end of the fourth week seems significant.

The coincidental occurrence of positive blood cultures and rose spots was frequently observed on admission; however the records of 2 cases show this relationship in a less casual way:

	DAY OF FIRST POSITIVE BLOOD CULTURE	FIRST DAY OF APPEARANCE OF ROSE SPOTS
1.	4	6
2.	6	7

Stool Cultures.—The appearance of typhoid bacilli in the stools occurred with great irregularity. In 16 cases in which stool cultures were started during the first two weeks of illness, the organism was never recovered. However, 50 per cent of all cases cultured during a similar period of the disease yielded the typhoid bacillus. In 5 cases positive cultures were obtained as early as the sixth day of the disease, and 50 per cent of 12 cases cultured during the first week of illness were similarly positive. The ease with which positive stool cultures may be missed is indicated by one case in which the cultures were negative on the fourth day, positive on the sixth day, and consistently negative after the eighth day. In a second case repeated cultures were negative until the twenty-fourth day of the disease and then were positive at irregular intervals for two weeks.

In a number of closely followed cases, cultures of the stools yielded no organism until after the end of the third week. In 5 cases in which no clinical recrudescence occurred, occasional positive stool cultures were obtained after the fifth week. In several instances single positive cultures were interspersed between several negative cultures.

The number of cases is too small to warrant any conclusions other than that the feces of typhoid patients may very early become a source of danger in the home, and early and repeated cultures should be taken in all cases. Although Derrison[11] rightly urges more frequent blood cultures, it is evident that the high percentage (85 per cent) of positive stool cultures, which he found in the third week, may offer a chance to make a diagnosis previously missed.

Urine Examinations.—The urine was cultured in only 7 cases. The 3 which yielded typhoid bacilli were positive in the second week. One was complicated by a *B. coli* superinfection. Over 50 per cent of all

cases showed a mild transient albuminuria. Casts and white blood cells were occasionally seen. One case showed gross pyuria (cultures negative) and in two instances moderate numbers of red blood cells were seen.

Widal Test.—The Widal reaction proved to be of diagnostic value surprisingly early in the disease. Of 52 cases admitted during the first two weeks of illness, 47 were analyzed. In 5 cases with negative serology on admission repeated Widal tests were not made. The reaction was positive during the first week in about 8 per cent, and during the first two weeks of the disease in 60 per cent of the cases. In only one case was there positive evidence that agglutinins were not present until during the fourth week. Too frequently a negative Widal reaction during the first week was not repeated until the fourth week, and no conclusions could be drawn from such cases.

COURSE

The disease in children is characterized by symptoms referable to the central nervous system, and of these the intractable irritability which renders some of the patients maniacal is perhaps the most distressing, for it interferes with every examination and every attempt to feed the child. The comatose patient can be tube fed; the irascible child with typhoid fever throws on the floor, spits out, or apparently intentionally vomits most of the food that is given it. With the fall in temperature the recovery from nervous symptoms occurred with delighting rapidity, except in two instances in which a period of stupor followed the fall of the temperature. In no instance did we observe a permanent insanity such as has been reported by Edsall[12] or the prolonged motor impairment observed by Chu and Tso.[13] One case, which was complicated by a superimposed staphylococcus septicemia, showed terminal convulsions, but while several writers[2, 6] have reported convulsions in uncomplicated cases, we felt that in the present situation the cause of the convulsions could not be defined.

TABLE V

NERVOUS SYMPTOMS

SYMPTOM	NO. OF CASES
None	9
Drowsiness	17
Headache	17
Irritability	14
Delirium	16
Irrationality	6
Stupor	5
Painful or stiff neck	5
Coma	7
Twitching	1

Lumbar punctures were done in 5 cases, and negative results obtained in 3 of them. The other 2, however, showed positive (Pandy)

tests for globulin. In one case bilateral Babinski reflexes and ankle clonus were present; in a second, positive Kernig signs were elicited, and clonus alone in a third.

Bronchitis.—Bronchitis was harassing in only one case but was diagnosed, either by physical signs or x-ray, in 20 cases. Pneumonia is recorded among the complications.

Pulse.—Although the true bradycardia observed in many adult cases was not found during the febrile period, the pulse was frequently relatively slow in comparison to the height of the fever. In 62 per cent of the cases pulse rates were in excess of 120 per minute at the time of admission. In only 1 case was the rate below 100 per minute on entry. When, however, as occurred with some frequency, particularly among the older children, a pulse rate of 100 to 110 per minute was charted with a temperature of 103 to 105° F., a relative bradycardia was recognized. Repeated observations showed marked fluctuation in rate, and swings from 110 to 150 per minute were not uncommon. With the end of fever the pulse rate frequently dropped below 90. In only one instance was dicrotism noted. Schlieps,[14] in cardiosphygmographic studies on 100 children with typhoid fever, found pronounced dicrotism only in children over fourteen years of age. He felt that true bradycardia was an almost constant finding at the beginning of convalescence.

Temperature.—The height of fever was generally between 103 and 105° F. The duration of fever in apparently uncomplicated cases varied from one and one-half to seven weeks. Two of three infants studied had less than two weeks of elevated temperature, and 50 per cent of 54 patients had less than three and one-half weeks of fever. Practically all writers have agreed that the course of the disease in children is considerably shorter than it is in adults.

The type of fever was of interest; plateau and irregular temperature curves occurred with equal frequency. Both types subsided by lysis and were frequently succeeded by days or weeks, during which the temperature fluctuated between 97 and 100° F. In one uncomplicated case, a truly septic type of fever prevailed. Ager[15] mentions the occasional occurrence of a temperative curve which simulates that seen in malaria.

Bowels.—Constipation and diarrhea occurred with equal frequency; the diarrhea, however, usually lasted but one to three days, whereas constipation was obstinate. Miller[16] has reported 2 cases of intestinal obstruction due to impaction of constipated feces in patients convalescent from typhoid fever, and, if proper attention were not paid to evacuation of the bowel, the degree of obstipation frequently seen might well effect such a complication. Six cases had both constipation and diarrhea. Of note, are the 14 cases in which there was apparently no disturbance of normal bowel habit.

Distention was common and occasionally troublesome. Of particular interest was the case of a previously obstipated and distended child with congenital megacolon, who during her disease and convalescence for the first time had a frequency of bowel movement approaching the normal one.

Blood-streaked stools were observed four times; tarry stools twice, and gross hemorrhage once. Gastrointestinal hemorrhage is obviously rare; this infrequency is presumably due to the fact that the intestinal ulcerations are much more superficial than those found in adults.[2, 6, 8]

Recrudescence.—Recrudescences occurred in 4 cases, and in general followed a similar, though shorter, course than the original fever. During the latter part of the second or early part of the third week the temperature fell to normal. After an interval of four to eight days fever reappeared. During the recurrence fresh crops of rose spots appeared, and the blood cultures again became positive. The type of temperature curve did not necessarily parallel that of the original bout of fever. The immunologic principles involved (or missing) in recrudescing typhoid fever have been studied by Thompson and Ecker[17] and others, but no conclusions can yet be drawn.

Complications.—The complications were essentially those of any protracted, febrile disease, and were largely pyogenic in character. The infrequency of cardiac complications is worth note and is in accordance with the observations of other writers. Adams[18] found but two instances of myocarditis and pericarditis among 550 cases of typhoid fever.

The occurrence of complicating *Staphylococcus aureus* septicemia in two of three brothers sick with typhoid fever is without explanation; two of the boys recovered.

The accompanying tabulation does not represent the number of patients who suffered complications; for example, one patient had otitis media, mastoiditis, sinus thrombosis, and flexion contractures of the hips.

Mortality.—Three patients (5 per cent) died. One child, ten years of age, died on the fifth day in the hospital. His was a fulminating illness which began two weeks before entry with abdominal cramps, chills, fever, and epistaxis. He became delirious and then comatose. Postmortem examination showed, in addition to the usual findings, a typhoid cystitis. A second boy, aged eight years, died on the twelfth day of the disease with a complicating *Staphylococcus aureus* septicemia, parotitis, pneumonia, furunculosis, and otitis media. Autopsy showed only shallow intestinal ulcerations, the pyogenic lesions already mentioned, cerebral edema, and bone marrow necroses. An eleven-year-old child who died on the twenty-eighth day, after having had severe hemorrhages two days earlier, showed no gross bleeding point, but cerebral edema and myocarditis were found at autopsy.

Treatment.—The treatment was purely symptomatic. Hydrotherapy has been advised by most of the older writers, and more recently Bey[19] stressed its value in the treatment of meningism. Some of our patients have been quieted by cold wet sheets, but others have been made maniacal, and except for an actual trial we are without a method for selecting suitable cases. Mouth care is a trying but indispensable treatment, and the thoroughness of the ministration is of more importance than the medicament.

The bowels require constant attention, and, while a few physicians employ laxatives, the safer recourse is to enemas (every two days if necessary). The attempt to give mineral oil should not be made for fear of upsetting an already capricious appetite. Stupes, rectal tubes, and enemas will usually control distention.

Blood transfusion was employed in two instances for severe anemia, and on a third occasion a transfusion from a patient recently recovered

TABLE VI

COMPLICATIONS	NO. OF CASES
Otitis media	12
Furunculosis	5
Recrudescence	4
Mastoiditis	3
Parotitis (staphylococcus)	3
Pyuria	2
Strabismus (?)	2
Pneumonia	2
Septicemia (*Staphylococcus aureus*)	2
Myocarditis	2
Bullous impetigo (thirteenth day)	1
Cystitis (autopsy)	1
Sinus thrombosis	1
Flexion contractures (hips and knees)	1
Appendectomy	1
Peritonitis	1
Hemorrhage	1
Diphtheria (nineteenth day)	1

from typhoid was given. Rouèche[20] on small experience has strongly advocated immunotransfusions; probably beneficial results may be expected in some cases. The more recent suggestion of Stokes[21] and others of using lyophile serum probably holds more promise.

The treatment of typhoid patients is essentially a nursing problem. Fortunately the duration of fever in children is relatively short, so that even with the usual refusal of adequate nourishment, severe emaciation is rare. Because of the benignity of the intestinal ulcerations in children, many observers have felt that the choice of food need not be restricted to the so-called "typhoid soft diet." Some writers warn specifically against milk and claim that the hard curds are more liable to do damage than softer solid food masses. Other writers ad-

vise giving the patients mixed diets;[22] the latter view seems reasonable and safe, and it is interesting that for some time one of our patients would eat nothing but macaroni and hard Italian bread.

Hospitalization.—Seventy-four per cent of the cases remained in the hospital over four and one-half weeks; 50 per cent of all cases were discharged during the fifth or sixth week.

Source.—It was extremely difficult in most cases to obtain any epidemiologic information, but the following sources are suggestive of the possibilities encountered:

Typhoid in the family	7 cases
Questionable carrier in the family	2 cases
Children at school with typhoid	1 case
Questionable typhoid vaccine	2 cases*
Questionable milk (milk handler had typhoid)	1 case
Well water	5 cases
Questionable raw clams	1 case
Neighborhood cases	1 case

Diagnosis on Admission.—The diagnoses considered, to the exclusion of, or together with, typhoid fever, and the numbers of times they were recorded are as follows:

Pneumonia	7
Meningitis	7
Tuberculosis	5
Septicemia	4
Appendicitis	4
Observation	3
Poliomyelitis	2
Dysentery	2
Pyelonephritis	2
Malaria	1
Influenza	1
Peritonitis	1
Encephalitis	1
Food poisoning	1
Tonsillitis	1

In 14 cases (23 per cent) typhoid fever was not considered at the time of the admission of the child to the hospital, and probably this was frequently due to the difficulties of taking a satisfactory history. Hand and Gitting[6] have written aptly ". . . . in some cases most diligent questioning can elicit nothing of value; and often the parents are of foreign birth and no richer in their knowledge of English than in the coin of the realm." When such a situation exists, we must rely on the unexplained fever, the neurologic signs, the rose spots, the splenomegaly, or the leucopenia to point out the need for blood and stool cultures and Widal tests.

*One brother died of typhoid fifteen days before onset of patient's illness. The father, older brother, and older sister received no inoculations and remained well. The mother and four boys received typhoid inoculations from an out-of-town physician three days prior to the onset of the patient's illness. On the second day after inoculation the mother and two brothers were admitted to the Massachusetts General Hospital with typhoid fever, and on the third day the two remaining brothers were admitted to this hospital.

SUMMARY

1. An analysis of 60 cases of typhoid fever in infants and children is presented.

2. Abdominal pain is prominent at the onset of 50 per cent of cases.

3. The white blood count may be high during the early stage of the disease; the leucopenia apparently appears just after the blood stream is invaded.

4. The appearance of typhoid bacilli in the stools occurs with great irregularity in single cases.

5. The Widal is positive by the end of the second week in 60 per cent of the cases.

6. The disease in children is characterized by an abrupt onset, the frequent appearance of neurologic symptoms, and a shorter course and lower mortality rate than is found in adults.

7. The complications are largely pyogenic. Hemorrhage and perforation are rare, and this rarity is presumably due to the superficial character of the intestinal ulcerations.

8. In the majority of sporadic cases the source cannot be determined.

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1002 North Mariposa

THE TREATMENT OF GONORRHEAL VULVOVAGINITIS WITH A SPECIAL GLUCOSE TABLET

PRELIMINARY REPORT

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FOLLOWING Allen's[1] experimental work with estrogenic substances on immature monkeys, Lewis[2] demonstrated the practicability of their use in the treatment of gonorrheal vulvovaginitis. While there has been disagreement since as to the therapeutic value, all are agreed that with their use a definite change from the childhood or infantile type to the adult type takes place in the vaginal mucosa. No mention, however, has been made as to the change in the hydrogen ion concentration of the secretion or change in the vaginal cervix. TeLinde and Brawner[3] obtained excellent results using an amniotin suppository and concluded that their results were due in most part to the estrogenic substance. Cruickshank[4] demonstrated in vitro that the vaginal bacteria are capable of converting glucose into lactic acid and produce a hydrogen ion concentration reaching 4.5.

With this in mind it was thought that if a glucose tablet were used as a suppository, the bacteria of the vaginal vault might convert it into lactic acid, producing the adult type of reaction and inhibiting the growth of the gonococcus. A tablet, small enough for insertion, composed of a carbohydrate, boric acid, and a small amount of arsenic was used. The carbohydrate was partially modified by oxidation and hydrolysis. The tablets were inserted night and morning and placed as far in the vaginal vault as was possible. No other treatment, except cleansing saline douches when the discharge was profuse, was used. All children were hospitalized in a special home maintained by the city for the treatment of vulvovaginitis. Once a week a 2 per cent lactic acid douche was given and an endoscopic examination was made to determine the progress. Smears were taken when necessary. An attempt was made in the early stages to dilate the vaginal outlet to promote better drainage. A determination of the hydrogen ion concentration was made using methyl red as an indicator. In a very short time pH 4.5 was produced, and it remained at this figure as long as treatment was continued. After treatment the reaction shifted quickly to the alkaline side. The discharge that was at first a dirty yellow changed to a white chalky color. The external meatus took on a pinkish to red color. No burning or itching was noted. Treatment was continued until the vaginal wall and cervix showed definite clinical improvement. Treatment was then discontinued and discharge smears, both cervical and vaginal, were started. No treatment was given while the smears were being taken. Three successive weekly

negative smears were obtained before the patient was discharged. The cases were checked at three weeks after discharge and then at periods of six weeks.

In Houston we have an institution whose specific purpose is the care and treatment of gonorrheal vulvovaginitis among the indigent children of the city. The patients are housed, clothed, fed, and taught while under treatment. The average age in the home is 7.5 years. Their nutritional and vitamin needs and general health are watched and correction made where necessary.

RESULTS

In January, 1936, treatment with glucose tablets was begun in twenty-four cases. In March, 1936, fifteen additional cases were added to the series. Nineteen patients have been discharged as cured with negative clinical and laboratory findings. All cases are being followed, and to date only one patient has been readmitted. This patient is thought to have had a reinfection. All thirty-nine cases showed vaginal and cervical involvement, as shown by smears. Previously the average number of days for a cure was 249.8. The average number of days required for patients receiving only the glucose tablets was 98.5. Eleven patients were in the home when glucose treatment was started. All eleven were considered chronic cases, failing to respond to any type of treatment. The average age for the group was 7.5 years. Two cases were complicated by proctitis, which cleared with treatment. No eye infection has occurred to date.

Although this series is small, we feel that with this type of treatment a step has been made in the control of gonorrheal vulvovaginitis. It is not the idea of this report to try and replace the hormone treatment. We believe that, if the glucose treatment were coupled with the hormone treatment, still better results would be obtained. Due to lack of funds we have been unable to carry out the combined treatment.

SUMMARY

1. A preliminary summary of a new type of treatment for gonorrheal vulvovaginitis is presented in which a special hydrolyzed glucose tablet was used.

2. Thirty-nine patients have been treated, and nineteen have been discharged as cured. The remainder are still under treatment.

3. Combining the estrogenic substances with the glucose tablets in the treatment of gonorrheal vulvovaginitis is suggested.

We wish to express our thanks to the Winthrop Chemical Company for their support in the carrying out of this work and to Dr. Karl Karnaky for helpful suggestions and cooperation.

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ENDOCRINE OBESITY IN CHILDREN: CLINICAL AND LABORATORY STUDIES AND RESULTS OF TREATMENT

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OBESITY in infancy and childhood may be due to exogenous or endogenous factors. The former type is generally due to overeating whereby the caloric intake greatly exceeds the caloric requirements. The endogenous factors are disturbances of the thyroid, pituitary, adrenals, and sex glands. Without entering into any discussion as to the relative etiologic importance of the anterior pituitary lobe, the posterior pituitary lobe, the tuber cinereum and the entire midbrain region to obesity, we may state that the most frequent causes of endocrine obesity in children are hypothyroidism and hypopituitarism. These may be subdivided into the following groups:

I. Primary hypothyroid obesity
   A. Onset during infancy
   B. Onset during childhood

II. Primary hypopituitary obesity
   A. Onset during infancy
   B. Onset during childhood or adolescence

III. Mixed types (thyropituitary obesity)
   A. Thyroid and pituitary
      1. Primary hypothyroidism with secondary hypopituitarism
      2. Primary hypopituitarism with secondary hypothyroidism
   B. Primary or mixed thyroid and pituitary forms with
      1. Normal genital growth
      2. Retarded genital growth (adiposogenital dystrophy, Fröhlich's syndrome)
      3. Normal somatic growth
      4. Abnormal somatic growth
   C. Primary or mixed types with involvement of the adrenal and/or the sex glands.

The hyperpituitary type, recently described by Cushing[1] as being due to basophilic adenoma of the anterior pituitary lobe, is characterized by rapidly acquired adiposity confined to the face, trunk, and neck without involving the extremities, sexual dystrophy, hirsutism

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of the face and trunk, hypertension, typical bone changes, and hyperglycemia. It is rarely found in children.

The adrenal type is also rare in children. It is due to hyperplasia or neoplasm of the adrenal cortex and occurs in two forms: the obese in the female child and the Herculean in the male. Infants may be fat and puffy with a predilection of the obesity for the abdomen, chest, buttocks, and hips.

Obesity due to hypogonadism is never observed at birth and seldom in childhood. The general appearance is that of tall graceful individuals with localized fat distribution on the outer thighs, hips and hypogastric regions.

In a study of several hundred cases of obesity in infants and children, we found the following points to be of value in the differential diagnosis between the thyroid and pituitary types:

	HYPOTHYROID	HYPOPITUITARY
History	Delay in teething, walking and talking if onset of obesity occurs prior to one year of age. Delay in eruption of second dentition. Birth weight may be above or below 8 pounds. Greater tendency to lose weight after the first year.	Normal development or premature eruption of first and second teeth. Birth weight may be above or below 8 pounds. Increased weight may continue or appear after illness or at puberty.
Physical characteristics	Generally short in stature. Broad typical face.	Normal, increased or diminished stature. Tendency to female contour in boys. "Angelic face."
	Universal distribution of fat with tendency to localization in supraclavicular regions.	Predilection for fat distribution seen in mammary, subscapular, abdominal, suprapubic, and trochanteric regions. Extremities not involved.
	Sexual development generally delayed in primary infantile form. May or may not be normal in other types.	Generally delayed sexual development in both sexes.
	Teeth are short, thin, malocclouded and tend to decay.	Teeth are well formed, thick, and of good consistency. Large with normal somatic growth, short in stunted growth. Central incisors are large, lateral incisors are small.
	Fingers are short but do not taper.	Tendency to tapering fingers.
	Skin and hair are dry. Polyuria and polydipsia are not present.	Skin and hair are soft. Polyuria and polydipsia are present.
Mentality	Varies from slight impairment in mild hypothyroidism to marked retardation in childhood myxedema.	Behavior more affected than mentality.
Bone development	Retarded in infantile primary hypothyroidism depending upon degree of deficiency and age of onset.	Normal carpal development. Epiphyseal union retarded in hypogonadism.

Basal metabolic rate	Low	Normal but may be low with deficiency of thyrotropic hormone of anterior pituitary lobe.
Specific dynamic action	Normal	Absent or diminished.
Blood chlorides	Normal	High (above 500 mg./100 c.c.)
Blood uric acid	Normal	High (above 3.5 mg./100 c.c.)
Blood cholesterol	High (above 200 mg./100 c.c.)	Normal (150-200 mg./100 c.c.)
Blood sugar	Low fasting blood sugar. Increased sugar tolerance.	Low fasting blood sugar. Increased sugar tolerance.
Salt retention	May or may not be present.	Generally marked.
Water retention	May or may not be present.	Generally marked.

MATERIAL AND SCOPE

The present communication reports the clinical and laboratory findings and the results of treatment of endocrine obesity in 50 children, 29 boys and 21 girls with the following age distribution: five years, 1; six to ten years, 12; eleven to fourteen years, 29; and fifteen to seventeen years, 8.

Each patient was studied in accordance with the methods and procedure described elsewhere,[2] which in brief are as follows:

1. A history of the family and patient with special reference to physical and mental development and incidence of illness, particularly to the age at the onset of obesity.

2. Physical and mental examination.

3. Laboratory and chemical studies including estimation of blood content of chlorides, cholesterol, sugar, uric acid, urea nitrogen, and creatinine; salt and water retention; basal metabolism and specific dynamic action of proteins; x-ray examination including the study of bone development and sella turcica. Serologic examination and sugar tolerance tests when indicated.

Every patient in this series was under observation and treatment at least twice a week for periods ranging from six months to one year.

Types.—The incidence of the various types of obesity in this series, as based on the differential diagnosis table, is as follows:

1. Hypothyroid, 12 per cent (primary hypothyroid, 8 per cent; with secondary hypopituitarism, 4 per cent).

2. Hypopituitary, 86 per cent (primary hypopituitary, 48 per cent; with secondary hypothyroidism, 38 per cent).

3. Primary hypogonadism (female), 2 per cent.

These figures indicate that pituitary obesity with or without secondary hypothyroidism (adiposogenital dystrophy and thyropituitary obesity) is the most frequent form occurring in children and that the primary hypothyroid and primary hypogonad types are the least frequent.

Family History.—There was a history of obesity in some other member of the immediate family in 20 per cent of the children.

Weight.—The birth weights in 40 children with available information show the following distribution: 11 were above 9 pounds; 8 were between 8 and 9 pounds; and 5 were below 5 pounds. The average was 7.6 pounds. These findings agree in general with figures obtained in another series in which we found that in 117 children with the pituitary or thyropituitary types of obesity, the birth weight was above 8 pounds in 66 cases and below it in 51 cases and that in 25 children with childhood myxedema or hypothyroidism in only 10 was the birth weight more than 10 pounds.

Our figures indicate that a natal weight of 8 pounds or more may occur with either hypothyroidism or hypopituitarism. The macrosomia, hyperadrenal type of Christiansen,[3] and that of fetal hypoglycemia are rare. Our findings are at variance with those of Engelbach,[4] who states that a birth weight of 8 pounds or above is pathognomonic of hypothyroidism. According to him, pure hypopituitary obesity is infrequent in infancy, and is characterized by a birth weight of 7 pounds or less and a sudden increase in weight between the fifth and sixth years. He feels that a persistent obesity from birth signifies a primary hypothyroid condition with an added hypopituitary element later.

The actual weight of the children in this series is as follows: above 200 pounds, 2 cases; between 199 and 150 pounds, 8 cases; between 149 and 100 pounds, 31 cases; and below 100 pounds, 9 cases.

For the purposes of this study the weight is considered from the viewpoint of percentage overweight of the patient in relation to his or her weight in comparison with the standards of Baldwin.[5] The results of treatment are evaluated by the difference between the initial and terminal percentage overweight as compared with the standard weight for the initial and terminal height and age. In other words, we take into consideration the added weight and height that accrue with an increase in age. In children it is manifestly improper to gauge by weight alone or by percentage overweight as compared to the initial height.

All patients in this series were overweight before treatment was instituted. The average initial overweight was 44.4 per cent. One child was 9 per cent overweight, 4 were between 10 and 19 per cent overweight, and the remainder were between 30 and 100 per cent overweight, except for one girl, eleven years of age, who was 143 per cent overweight.

The previous history of the weight curves in this series show the same tendencies observed by us in larger groups of children with endocrine obesity. They are (1) initial birth weight of 8 to 9 pounds

or above with a steady increase, (2) a drop to normal levels and a subsequent rise which may occur spontaneously or after an acute infection, (3) a sudden increase in weight either spontaneously or following illness or trauma in a child who was previously thin or normal in weight, or (4) a sudden spurt in weight at the time of puberty. The obese child of the primary infantile hypothyroid type tends to lose weight very early in childhood and is not as frequently observed as the pituitary or mixed type. In two cases of this type, the children were obese at birth, lost weight in infancy, and regained it during childhood.

There is an apparent relationship between the onset of obesity and the occurrence of illness, trauma, and operation in this series. Of 33 cases with available information, the onset of obesity and increased weight followed tonsillectomy in 7 instances, appendectomy in 3, trauma in 2, measles in 2, and chickenpox and whooping cough in 1 each. Obesity was present since birth in 15 and occurred at puberty in 2.

Distribution of Fat.—The distribution of fat followed in general that described under the differential diagnosis. One girl with primary eunuchoidism showed a trochanteric type of obesity.

Height.—In accordance with Baldwin's standards, the children in this series fall into the following groups: normal average medium height for age, 8; above average medium height for age, 25; below average medium height for age, 17. If grouped according to the upper and lower levels of normal height of Baldwin's tables in place of the average medium, 37 children are within the limits of normal height for age; 8 are above the average tall height for the age; and 5 are below the average short height for age.

Sex Development.—Of the 29 boys in the series, 2 showed normal sex development, and 27 showed secondary hypogonadism. Of the latter, 15 showed descent of the testes, 7 bilateral cryptorchidism, and 5 unilateral cryptorchidism.

Of the 16 girls at the age of puberty, there is a history of normal menstruation in 7, irregular menstruation in 4, secondary amenorrhea in 4, and primary amenorrhea (eunuchoidism) in 1.

Chemistry.—In discussing the chemical and other laboratory findings in this series, we wish to emphasize that, in general, all nonendocrine conditions must be eliminated before any finding can be considered as being due to endocrine disturbance.

The following methods were used for the determination of the respective constituents of the blood: glucose (Folin and Wu); urea nitrogen (Folin and Wu); creatinine (Folin and Wu); uric acid (Benedict); chlorides (Whitehorn); cholesterol (Bloor).

The salt retention test is carried out as follows: the usual diet and fluid intake of the patient are taken for twenty-four hours and the amount of sodium chloride in the urine is measured. (A more precise method would be to give a standard diet and fluid intake for several days until the amount of sodium chloride excreted in the urine is fairly constant.) On the following day, the same diet is taken. After breakfast is finished, 10 gm. of salt are taken in capsules or in raspberry juice. The urinary volume and sodium chloride content are measured, and the salt retention computed. According to most authorities, if the individual has been on a well-balanced diet all or most of the salt under normal conditions will be excreted in the urine in twenty-four hours. If, however, he has been on a salt-poor diet, the salt will be taken up by the tissues and very little will be excreted in the urine.

Water retention was determined by measuring the urinary volume before and after the ingestion of 10 gm. of salt. This should be followed by an increase in urinary volume. The method of Vollhard* may also be used in measuring the degree of water retention. As it is difficult to tell to what extent retarded urinary excretion is due to tissue retention or to a diminution in the salt-excreting capacity of the kidneys, all possible nonendocrine factors, especially renal, must be eliminated.

The findings of each chemical constituent are shown in Table I. The figures indicate that obesity in children is associated with high values of blood chlorides, uric acid and cholesterol, low normal values of sugar, normal values of urea nitrogen and creatinine, and also salt and water retention.

Our findings of high blood chloride contents and salt retention confirm the experimental and clinical findings of others[6] and tend to show that the pituitary gland may have an influence, direct or indirect, on chloride metabolism. High blood uric acid values (above 3.5 mg. per 100 c.c.) have been reported by Rowe[7] in pituitary disturbances. All but one of the four instances of values below 3 mg. in our series occurred in children with primary hypothyroidism.

There are thirteen instances of blood cholesterol values above 200 mg. per 100 c.c. of blood, the highest (254 mg.) being found in a girl with primary childhood hypothyroidism. The average value of 189.6 mg. per 100 c.c. of blood is higher than that obtained in a larger group but this may be explained upon the presence of a larger incidence of hypothyroidism in the present series (55 per cent with a basal metabolic rate of below 10 per cent). In these thirteen cases with values of 200 mg. or above, there is a range in the basal metabolic rate be-

*The patient drinks one liter of water in the morning within one hour; during the following four hours the urine is voided at one-half-hour intervals. In healthy individuals practically the entire amount is voided within that time, most of it within the first hour or hour and a half.

tween –3 and –33 per cent in twelve and a reading of +12 per cent in one. The average basal metabolic rate for the group is –17 per cent.

There does not seem to be much variation in the blood sugar values between the thyroid and pituitary types. There are 14 patients with a value of 50 mg. or less.

TABLE I

LABORATORY FINDINGS IN ENDOCRINE OBESITY IN CHILDREN

BLOOD CHEMISTRY	NORMAL VALUES (MG./100 C.C.)	AVERAGE VALUES IN THIS SERIES (MG./100 C.C.)
Sugar	70-120	89.3
Urea nitrogen	12- 15	13.3
Creatinine	1- 2	1.27
Uric acid	2- 3.5	4.38
Cholesterol	150-180	189.6
Chlorides (as NaCl)	450-500	505.1
URINE		
Average NaCl content in 24-hour urine before ingestion of NaCl*		6.9 gm.
Average NaCl content in 24-hour urine after ingestion of 10 gm. NaCl		10.4 gm.
Average NaCl retention (65 per cent)		6.5 gm.
Average volume of urine in 24 hours before ingestion of NaCl		828.0 c.c.
Average volume of urine in 24 hours after ingestion of 10 gm. NaCl		1,032.0 c.c.
Increased volume of urine		24.7 per cent

*The normal excretion of NaCl in urine is given by most authorities as 10 to 15 gm. daily.

METABOLISM		
Basal metabolic rate		
Below –10	55	per cent of cases
–10 to +10	41	per cent of cases
Above +10	4	per cent of cases
Specific dynamic action		
Specific dynamic action of 0	42	per cent of cases
Below 10	79	per cent of cases
Average specific dynamic action	4.1	

Metabolism.—There is no unanimity in the literature as to the basal metabolism in obesity, either as to the rate or as to the basis of calculation. Upon the basis of actual weight, a reading of below –10 was obtained by Engelbach[4] in 21 out of 39 children and adolescents and by Rony[8] in 14 out of 42 children. Kenyon[9] noted a rate of –15 or below in 8 out of 50 patients.

Evans and Strang[10] claim that the rate should be computed on the basis of ideal weight instead of on the actual. If so calculated, many patients will show an increased instead of a decreased metabolic rate as the extra weight is due to inert fat which does not take part in the active metabolism of the body. On this basis, they found the basal metabolic rate to be between +20 and +25 per cent in the majority of

187 obese subjects and below the normal in only 2 per cent. Dunlop and Lyon[11] also noted the same tendency, obtaining a low rate in only 8.3 per cent of 523 obese individuals.

The results of metabolic studies in the present series on the basis of actual weight are presented in Table I. A basal metabolic rate lower than –10 was obtained in 55 per cent of the children distributed as follows: boys, 59 per cent; girls, 50 per cent. The lowest basal metabolic rate was minus 33 per cent.

The specific dynamic action was studied according to the modification of Goldzieher and Gordon.[12] In our first series of 41 cases of obese children,[12] we obtained a specific dynamic action of zero in 40.6 per cent of the children and of below 10 in 81.3 per cent. The average value for the group was 4. Almost identical figures are found in the present series in 43 children. The specific dynamic action in normal children is 10 to 25.

TREATMENT

The treatment of endocrine obesity used in this series is as follows:

1. Dietary regulation: Children are given, on the average, a diet of about 1,000 calories a day with high protein, low fat, low carbohydrate, and adequate vitamin content. Salt and water intakes are restricted.

2. Oral administration of thyroid and pituitary extracts was as follows:

	FIRST MO.	SECOND MO.	THIRD MO.	FOURTH MO.
Desiccated thyroid gland	gr. ⅛	gr. ¼	gr. ½	gr. i
Desiccated anterior pituitary gland	gr. ii	gr. iii	gr. iv	gr. v

These extracts were given three times a day for the first three weeks of each month and discontinued for the fourth week.

3. Hypodermic injections of anterior pituitary extract, 1 c.c. twice a week.

4. In all cases of cryptorchidism and in protracted cases of hypogonadism in males, extract of pregnancy urine, 1 c.c. twice a week, is substituted for the anterior pituitary extract mentioned above. In stubborn cases a combination of 1 c.c. each of anterior pituitary extract and pregnancy urine extract twice a week may be given.

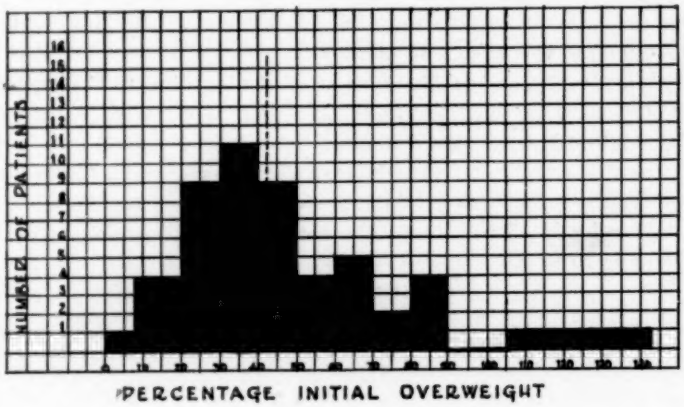
5. In female hypogonadism, a combination of anterior pituitary extract and female sex hormone, 1 c.c. each, is administered twice a week.

6. Accessory treatment: Pituitrin intranasally may be beneficial in refractive cases of polyuria and polydipsia.

A skimmed milk diet may be given one or two days during the week or mineral oil may be administered before meals to slow absorption in refractive cases of obesity and stationary weight.

CRITERIA FOR IMPROVEMENT

Loss of weight, redistribution of fat from areas of predilection, increase in growth and height, and amelioration of endocrine symptoms: basal metabolism, specific dynamic action, hypogonadism, cryptorchidism, etc.



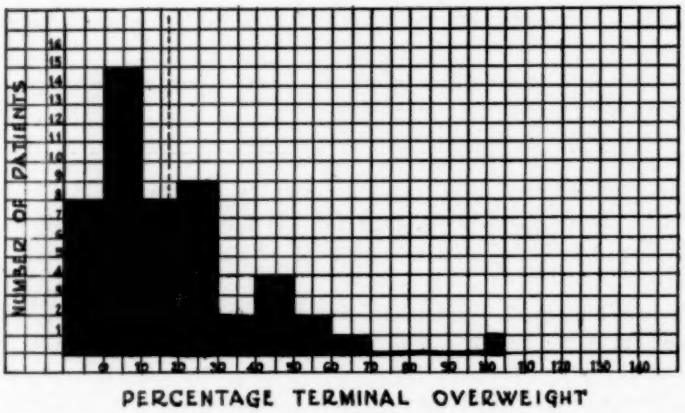


Fig. 1.—Distribution graphs showing percentage of overweight before and after treatment.

RESULTS

Weight.—The effects of treatment on weight are demonstrated graphically in Fig. 1. As explained previously, the percentage of overweight is based upon the height and age at the time of inception and completion of treatment. The average overweight was 44.4 per cent before treatment and 18.8 per cent after treatment. Prior to

the institution of treatment there was only one child who was 9 per cent overweight, but after the completion of treatment 8 children were not overweight, and 15 were from 1 to 9 per cent overweight. In other words, practically one-half of the number of children were reduced to within 10 per cent overweight for their height and age.

There was an average difference of 25.6 per cent between the initial and terminal overweight. The difference ranged from 1 to 19 per cent in 15 cases, from 20 to 39 per cent in 28 instances, and from 40 to 70 per cent in 6 patients. One child showed an increase of over 5 per cent.

The initial loss of weight is as follows: average loss of weight for those over 200 pounds, 28 pounds; average loss of weight for those between 150 and 200 pounds, 28.8 pounds; average loss of weight for those to 150 pounds, 11.7 pounds; average loss of weight in entire series, 15.1 pounds.

Height.—The average increase in height between the first and final examination is as follows: In those children with medium height for their age there was an average increase of 2.12 inches. In those below average medium height for their age the average increase is 1.82; the average increase for the entire series is 1.9 inches. The greatest increase is in the average medium height class and the least in the above height group.

Basal Metabolic Rate and Specific Dynamic Action.—We were able to study the effects of treatment on the basal metabolism in 23 cases. There was an increase of over 10 per cent in 10 cases and from 1 to 9 per cent in 10 instances. There was no change in 2 cases and a drop in 1 case. The average increase was 8.5 per cent. The basal metabolic rate was increased to normal limits (±10 per cent) in 8 children. There was no correlation between the percentage of reduction in weight and the difference in the basal metabolic rate before and after treatment.

Treatment produced an increase in the specific dynamic action of 10 per cent in 2 children and of 1 to 9 per cent in 11 instances; there was no increase in 4 children and a decrease in 1 child. Treatment apparently exerts a more marked effect on the lower levels than on the upper. In 8 patients with a specific dynamic action of 0, there was an average increase of 8.6 per cent; in 6 children with specific dynamic action figures of from 1 to 9 per cent, there was an average increase of 4 per cent; and in 6 patients with specific dynamic action percentages of 10 or above, the average increase was only 1.5 per cent.

Sex Disturbances.—The treatment for girls consisted of oral administration of desiccated thyroid and anterior pituitary substances and hypodermic injections of female sex hormone with or without anterior pituitary extract. In some instances the female sex hormone was given for the first three weeks of each month and anterior pituitary-

TABLE II

RÉSUMÉ OF FINDINGS IN WEIGHT, HEIGHT, AND METABOLISM

NO.	AGE (YEARS)	SEX	WEIGHT (LB.)		HEIGHT (IN.)		PERCENTAGE ABOVE AVERAGE WT. FOR HT.		DIFFERENCE IN PERCENTAGE OVERWEIGHT AS RESULT OF TREATMENT	ACTUAL OXYGEN CONSUMPTION IN C.C. PER MINUTE		B.M.R.	
			INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL		INITIAL	FINAL	INITIAL	FINAL
1	10	F	108	97	58.50	59.25	25	8	17	177	197	-26	-11
2	14	F	143	126	59.50	59.50	47	28	19	188	—	-16	—
3	17	F	114	106	52.25	52.50	70	58	12	176	—	12	—
4	9½	M	89	78	54.00	55.50	27	5	22	149	180	-30	-13
5	10	F	102	86	56.00	58.00	31	0	31	181	167	-12	-18
6	14½	F	192	155	65.00	65.50	58	27	31	264	280	- 4	6
7	13	F	148	131	66.00	66.50	19	2	17	257	—	1	—
8	11½	M	121	104	59.00	61.00	36	7	29	169	200	-22	-15
9	10	M	114	89	56.25	57.75	42	6	36	188	184	-20	-18
10	14	M	96	87	57.25	58.75	15	0	15	174	176	-20	-16
11	12	M	172	134	60.50	64.00	83	21	62	290	—	0	—
12	14	F	145	112	58.50	59.00	54	16	38	191	225	- 7	0
13	17	F	132	112	61.00	61.25	18	7	11	172	—	-19	—
14	10	M	93	100	54.00	55.25	32	37	+5	171	—	-19	—
15	14	M	143	124	63.00	65.75	32	0	32	185	238	-26	- 4
16	13½	M	144	169	60.00	63.56	55	54	1	246	—	- 4	—
17	10	M	95	85	55.50	57.75	30	1	29	217	—	0	—
18	17	F	141	123	62.25	63.00	20	3	17	205	—	- 5	—
19	17	M	224	206	64.00	64.00	85	63	22	285	—	- 5	—
20	11	M	112	103	58.00	61.00	33	7	26	—	—	—	—
21	8	F	82	66	53.25	56.00	22	0	22	130	158	-26	-18
22	14	M	154	126	60.25	61.50	64	26	38	200	265	-12	- 1

TABLE II—CONT'D

23	13	M	129	123	62.50	64.50	24	7	17	198	189	−22	−18
24	11	M	156	143	60.25	61.75	67	41	26	213	—	−24	—
25	11	F	145	127	58.25	64.00	70	10	60	178	218	−19	− 7
26	12	F	105	128	55.00	61.00	40	18	22	—	—	—	—
27	10	M	116	97	59.00	60.75	34	4	30	200	159	−18	—
28	16	F	192	155	62.25	64.00	67	29	38	232	—	− 3	—
29	13½	F	126	114	59.00	62.00	34	5	29	142	190	−33	—
30	11	M	133	117	60.25	61.50	44	16	28	208	202	−20	—
31	12	M	69	62	50.00	50.50	19	5	14	155	—	− 9	—
32	7	M	79	93	48.25	52.50	49	47	2	131	150	−31	—
33	13½	F	168	135	67.00	69.00	30	0	30	211	270	−11	—
34	12	F	243	205	60.75	61.00	143	103	40	303	—	4	—
35	12	M	123	103	60.50	64.00	31	0	31	—	—	—	—
36	12	M	107	99	58.25	59.00	26	11	15	198	237	−15	—
37	12	F	126	119	65.25	66.00	9	0	9	200	—	−17	—
38	5	M	68	54	43.50	45.25	66	17	49	157	153	− 8	—
39	10	M	103	91	56.50	58.75	32	4	28	—	—	—	—
40	16	F	129	120	59.00	59.00	25	11	14	159	—	−22	—
41	11	M	145	114	56.00	57.00	88	41	47	222	—	− 4	—
42	12	M	114	102	56.00	56.75	48	26	22	193	—	−15	—
43	16	F	175	146	61.00	61.00	56	30	26	270	—	10	—
44	10	F	108	95	55.00	55.50	46	27	19	172	—	−15	—
45	10½	F	132	121	59.75	60.25	42	5	37	232	—	− 3	—
46	13	M	130	116	58.50	59.50	49	27	22	227	—	− 2	—
47	14	M	116	103	58.50	59.50	24	12	12	—	—	—	—
48	11	M	112	108	59.25	64.25	21	0	21	190	—	−11	—
49	8	M	94	78	51.00	52.00	84	22	62	133	—	−25	—
50	15½	M	156	140	60.00	60.25	64	46	18	268	—	7	—

like extract of pregnancy urine in the fourth week. Beneficial results were noted in one out of four cases of irregular menstruation and in two out of four cases of secondary amenorrhea. In one case of primary amenorrhea due to eunuchoidism in a girl aged fourteen years, six months' treatment was followed by development of mammary tissue and increase in size of the gland, appearance of pubic and axillary hair, reduction in the amount of trochanteric obesity, and loss of weight. There was a continued improvement in the secondary characteristics during the following six months, but to date menstruation has not been established. There was a slight increase in height.

Improvement was noted in the majority of instances of hypogonadism in the male following the oral administration of anterior pituitary and thyroid substances and hypodermic injection of anterior pituitary extract. Extract of pregnancy urine was added only in stubborn cases of hypogonadism and in cryptorchidism. Improvement in hypogonadism was marked in 12, fair in 12, and poor in 3 cases. Complete descent of the testes resulted in all cases of bilateral cryptorchidism and in 3 out of the 5 cases of unilateral cryptorchidism. There was no effect in 2 instances of unilateral cryptorchidism.

The results on each component part of the external genitals were not uniform, i.e., enlargement of the phallus was not always accompanied by a beneficial effect on the testes or by a corresponding increase in the size of the scrotum. Improvement in the basal metabolism, specific dynamic action or general endocrine condition, and correction of obesity were generally, but not always, accompanied by the same degree of improvement in the hypogonadism or cryptorchidism. The relationship between sex disturbances and obesity is discussed more fully in a separate communication.[13]

Untoward Symptoms.—The administration of anterior pituitary extract was followed in several instances by one or more of the following: urticaria, angioneurotic edema, pruritis, abdominal cramps, and loose bowel movements. Anterior pituitary-like extract of pregnancy urine produced rashes and itching but no gastrointestinal symptoms. Acute congestion of the testes occurred in two instances of adiposogenital dystrophy with hypogonadism and immature testes after the injection of 6 and 10 c.c., respectively, administered in doses of 1 c.c. twice a week.

COMMENT

There is an intimate relationship between obesity, excessive food and fluid intakes, water and salt metabolism, and endocrine disturbances. There are numerous investigators who claim that overeating is the most important factor in the production of obesity and that overeating is entirely exogenous in nature.[9, 10, 11] Our experience has

been that overeating per se is an infrequent cause of obesity in children and that when there is overeating, it may be because of factors endogenous, exogenous, or both.

Excessive appetite may be either the cause or result of endocrine deficiency and imbalance. Frequent, repeated nibbling of sweets in small amounts, such as children are wont to indulge in, may cause repeated stimulation of the insulinogenic apparatus to aid in the oxidation of the added sugar. This hyperinsulinism may be accompanied by so-called abdominal hunger pains which in turn are relieved by the ingestion of food or more carbohydrates. This vicious cycle results in increased weight and obesity and in disturbed function of other members of the endocrine system, especially the pituitary.

Numerous experiments and clinical observations have demonstrated the relationship of water and salt metabolism to obesity and increased weight. The consensus of opinion seems to be that endocrine disturbances play an important rôle in this relationship, especially those of the pituitary, thyroid, and, to a lesser extent, of the pancreas. The posterior pituitary lobe exerts an influence either directly or indirectly on both salt and water metabolism. The thyroid mobilizes water and chlorides and promotes their elimination by the kidneys, an influence which is utilized in the treatment of nephrosis. The relationship of the pancreas is shown by the water retention following the injection of insulin and, on the other hand, by the polyuria associated with some cases of diabetes. Zondek[14] ascribes a cerebral origin to obesity associated with water and salt retention, without any relationship to the thyroid or pituitary.

Water retention is generally associated with salt retention, and increased water elimination with increased salt excretion. Exceptions to these general rules occur, as in our series, where we found instances of associated polyuria and salt retention and polyuria and water retention.

It is interesting to note that the sodium chloride content of the urine, irrespective of the urinary volume, was lower in our patients on their usual diet and water intake than that generally stated as normal for children. This diminished excretion and the high blood chloride content tend to show a salt retention in obese children which is confirmed by the salt test. Water retention is shown in our series by an increase in urinary volume of only 25 per cent following the ingestion of salt.

Treatment must take into consideration all of the factors discussed above.

In the diets published by Evans and Strang,[10] Kenyon,[9] and others of their school,[11] attention is focused on the low caloric intake with a high-protein, low-fat, and low-carbohydrate content. Water and

mineral salts are not restricted, and glandular extracts are not administered except in cases of definite hypothyroidism, in which event thyroid extract is given. Upon the basis of their results, these authors claim that obesity in children is due to exogenous factors, mainly overeating, and state that dieting alone will produce a redistribution of fat to normal locations and a reduction in weight which persists after the diet has been discontinued.

Our experience has been at variance with theirs. We have found that, while diet alone will produce a loss of weight and a reduction in obesity, this is true only for the duration of the diet and perhaps for a short time thereafter. The loss of fat is general and not from the areas of predilection. We have not observed any effects with diet alone on the associated endocrine conditions such as hypothyroidism, cryptorchidism, low basal metabolism, low specific dynamic action, constipation, "lack of pep," etc.

Because of the retention of both salt and water in obesity, it is a mistake to permit stout individuals to drink freely. Fluctations in weight commonly occur with the increase and decrease in water and salt consumption, especially when there is a tendency to a retention. In cases of epilepsy associated with obesity, an unrestricted water intake in conjunction with the administration of an antidiuretic, such as pituitary extract, may result in a marked retention and precipitate an attack.

Obesity is a manifestation of a general disturbance, and its treatment should be directed against the underlying cause, which we feel is mainly endogenous. Endocrine therapy is indicated in every case of obesity in childhood, but it should be supplemented by diet, and in the majority of cases by salt and water restriction. The best results are obtained by this combination and not by diet or organotherapy alone.

SUMMARY

Obesity in children may be due to exogenous or endogenous factors. In our experience actual overeating per se is an infrequent cause in children. The endocrine factors are disturbances of the thyroid, pituitary, adrenal, and sex glands. The thyroid and pituitary types may be divided into primary and mixed forms.

A table for differential diagnosis between the thyroid and pituitary types of obesity is offered; it includes consideration of history, physical examination, bone development, basal metabolism, specific dynamic action, blood chemistry, salt and water retention.

The present report analyzes the findings and results of treatment of 50 children with endocrine obesity who were studied with reference

to the factors enumerated above and who were observed for at least from six months to one year. There were 29 males and 21 females.

The etiologic types represented in the series are: (1) hypopituitary, 86 per cent (primary, 48 per cent—with secondary hypothyroidism, 38 per cent); (2) hypothyroid, 12 per cent (primary, 8 per cent—with secondary hypopituitarism, 4 per cent); (3) hypogonad (primary female), 2 per cent. These figures indicate that pituitary obesity, with or without secondary hypothyroidism (adiposogenital dystrophy and thyropituitary obesity), is much more frequent than the primary hypothyroid or the primary hypogonad types in childhood.

A birth weight of 8 pounds is found with either the pituitary or thyroid type. A child with the former tends to lose weight early and gain later. In the pituitary types there may be a steady gain in weight, a decrease and then an increase or sudden spurt in weight during childhood or at puberty. There seems to be a relationship between the time of onset of obesity and the occurrence of an acute illness, operation, or trauma.

The average initial overweight in this series was 44.4 per cent on the basis of height for age as compared with Baldwin's standards, ranging from 9 to 143 per cent overweight.

The majority of children were of average normal height for the age or taller. Only 5 were below average short height for age.

The sexual development was normal in 2 boys and retarded in 27. Cryptorchidism was present in 5 unilaterally and in 7 bilaterally. Menstrual disturbances were present in 9 girls of postpubertal age, including 1 with primary eunuchoidism.

On the basis of actual weight a basal metabolic rate below –10 was noted in 55 per cent of the children, between +10 and –10 in 41 per cent, and above +10 in 4 per cent.

The specific dynamic action is diminished in childhood endocrine obesity, according to our findings in this series and in earlier studies. In the present series the average specific dynamic action was 4.1. The values are below 10 in 79 per cent of the patients and 0 in 42 per cent.

Blood chemistry studies indicated that endocrine obesity is associated with high values of chlorides, uric acid, and high normal content of cholesterol (depending upon the degree of accompanying hypothyroidism), low normal values of sugar, and normal content of urea nitrogen and creatinine. Salt and water retention are present in the majority of cases.

The treatment, as carried out in this series, consisted of (1) low caloric diet, high in proteins, low in fat and carbohydrates, and restriction of salt and water intake; (2) oral administration of desiccated thyroid and anterior pituitary gland substances; and (3) hypodermic injection of anterior pituitary extract and hypodermic injec-

tion of extract of pregnancy urine or of female sex hormone in cryptorchidism and menstrual disorders and in protracted cases of hypogonadism.

Practically one-half of the number of children treated were reduced in weight to normal or to within 10 per cent overweight for height and age on the basis of accrued height. There was a redistribution of fat toward a more normal allocation and a general increase in height in spite of the low caloric diet.

There was an average increase of 8.5 in the basal metabolic rate for the series. It was increased to normal limits (+10 to −10) in one-third of the cases. There is no correlation between percentage reduction in weight and the difference in basal metabolic rates before and after treatment.

Treatment produced an increase in specific dynamic action, this apparently being more marked in the lower than in the upper levels.

Hypogonadism and cryptorchidism were benefited to a greater extent than menstrual disturbances in girls. The degree of improvement in the component parts of the external genitals (phallus, scrotum, testes) was not uniform. Results in the basal metabolic rate, specific dynamic action, obesity, and sex development were generally, but not always, parallel.

Untoward results noted during treatment consisted of urticaria, angioneurotic edema, pruritis, abdominal colic, and loose bowel movements. Acute congestion of the testes was noted in two instances of hypogonadism following the use of anterior pituitary-like extract.

Obesity is a manifestation of a general disturbance, and its treatment should be directed against the underlying causes, which we feel is mainly endocrine. The best results are obtained by a combination of organotherapy, a low caloric diet with high-protein, low-fat and low-carbohydrate content, water restriction, and salt restriction.

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EDEMA IN THE NEWBORN DUE TO PRELACTEAL FEEDING

Report of Four Cases

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THESE cases of edema were considered important enough to report because their occurrence indicates the need for some caution in the use of hydrating solutions for infants. This appears especially important in view of the interest in the use of hydrating solutions as prelacteal feedings to reduce the weight loss in newborn infants. Furthermore, the artificial (though in these cases accidental) production of edema is interesting in itself, and we hope that this report might give some helpful clues as to the mechanism of edema.

For several years 5 per cent lactose solution plus 0.5 per cent sodium citrate, as first recommended by Eder and Bakewell,[1] was used routinely at the Wesley Memorial Hospital. This mixture was offered to each infant every three or four hours during the first few days of life until there was adequate breast milk or an artificial feeding formula was started. Following that, for a period of some months, beta lactose was substituted in that formula instead of lactose. On both of these prelacteal feedings the initial weight losses were small and the subsequent gains satisfactory. The somewhat better results with beta lactose interested us in trying some other sugars. We tried dextrimaltose No. 1 with 0.5 per cent sodium citrate.

The results were spectacular, with the initial weight loss almost eliminated and with phenomenal weight gains in the first week of life. It was not until the first case of edema was closely followed by a second case that we realized that the dextrimaltose No. 1—sodium citrate solution could be causing the edema. We had, after all, been using a 5 per cent sugar solution with 0.5 per cent citrate for years with no ill effects. We were scarcely prepared for such different results simply with the substitution of another sugar, even though, as we rather tardily recalled, dextrimaltose No. 1 contains 2 per cent sodium chloride.

Case 1.—The first case of edema was in Baby J., who weighed 7 pounds, 5¾ ounces at birth. The birth was normal. He took fluids well beginning the first day of life. The infant was offered the routine 3 ounces of 5 per cent dextrimaltose No. 1 with 0.5 per cent sodium citrate every three hours. He ingested the following amounts in the first six days of life:

1st day—8½ oz. sugar solution
2nd day—15 oz. sugar solution
3rd day—17 oz. sugar solution and 3¼ oz. breast milk

From the obstetric and pediatric services of the Wesley Memorial Hospital, and Department of Pediatrics, Northwestern University.

Read before the Chicago Pediatric Society, March, 1936.

4th day—12 oz. sugar solution and 10 oz. breast milk
5th day—15½ oz. sugar solution and 12 oz. breast milk
6th day—8 oz. sugar solution and 13 oz. breast milk

On the sixth day the face, neck, and legs were edematous, the legs pitting on pressure. The edema remained the same for four days. The weight graph, Fig. 1, shows his astounding gains. The urine was negative. A complementary feeding of evaporated milk and water and dextrimaltose No. 1 was started on the seventh day. The prelacteal mixture was stopped except for 3 ounces, given at night on this and succeeding nights.

On the eighth day the blood chemistry was total nonprotein nitrogen 38.7; total protein 3.5 (albumin 1.5, globulin, 2). This was no increase over normal values. The urine had 5 mg. albumin per 100 c.c.

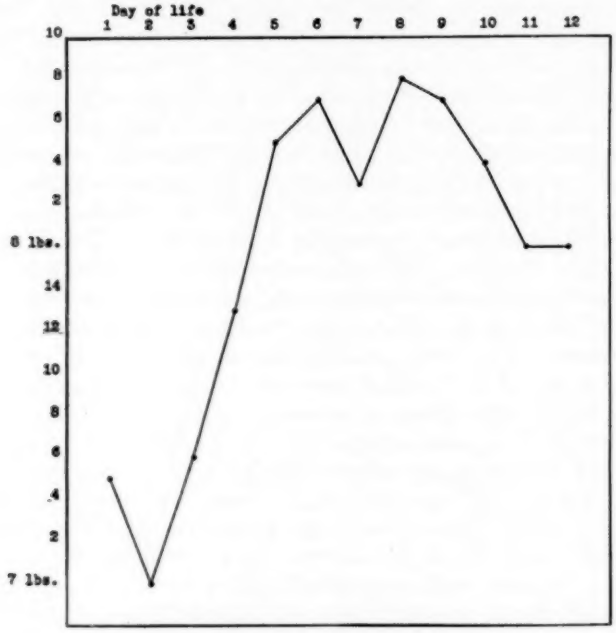

Fig. 1.—Weight chart of Baby J.

On the tenth day the urine had 25 mg. albumin per 100 c.c. On this day there were slight intermittent twitchings of the right arm and leg for several hours. The infant regurgitated for the first time, but only once. The edema receded somewhat during the following two days. The infant was discharged on the twelfth day. At this time the infant appeared in good condition, nursed well at the breast and bottle, but still had some edema of the extremities.

It seems reasonable to assume that the muscular twitchings were from irritation consequent upon cerebral edema. There was no carpopedal spasm nor Chvostek's sign. We reluctantly contented ourselves with the diagnosis of idiopathic edema of the newborn.

This infant was seen again several months later and was quite normal.

The second case occurred two weeks later.

CASE 2.—Baby M.'s birth was normal. He weighed 8 pounds, 6 ounces. He was active, cried vigorously, and nursed well. He was given the dextrimaltose No. 1—sodium citrate solution. He ingested 6 ounces of it the first day of life, 11½ ounces the second day, 13½ ounces the third day, and 15½ ounces the fourth day.

On the fourth day he took 8 ounces of an evaporated milk and water and dextrimaltose formula that was started on that day, as he had obtained only 4 drams of milk from the breast. On that day he had slight twitchings of the left arm and leg for one to two minutes at a time, several times during the day. That night he took 4 ounces of the dextrimaltose-sodium citrate solution, the milk formula being given only during the daytime. On the four following nights he took 2½ ounces, 4 ounces, 6 ounces, and 4¾ ounces, respectively, of the sugar and citrate

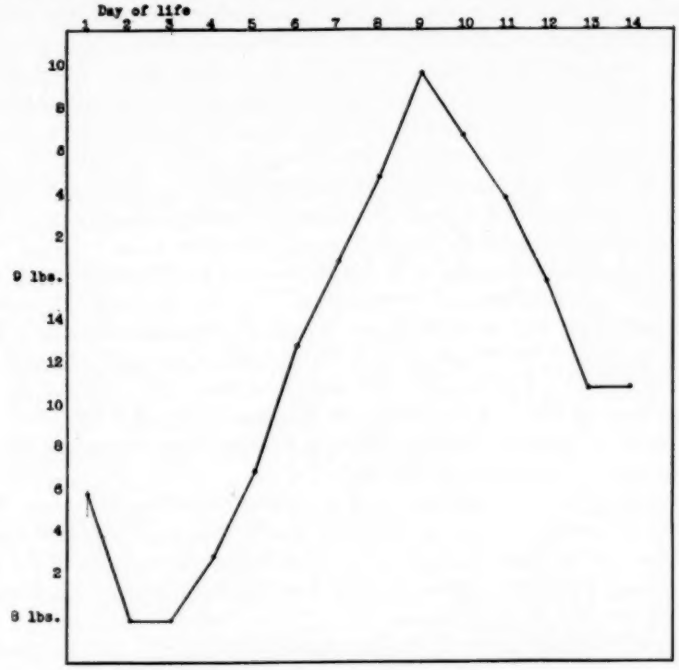

Fig. 2.—Weight chart of Baby M.

solution. The muscular twitchings on the fifth day were interpreted as evidence of possible cerebral hemorrhage, and he was given 8 c.c. of whole blood intramuscularly. Twitchings were noted three times on the following day and he was given 10 c.c. of whole blood. On the seventh day muscular twitchings were noted only twice. On this day there was edema of the legs with slight pitting on pressure. The urine was negative.

On the eighth day the edema was more marked involving the legs, scrotum, penis, and abdominal wall with a beginning edema of the face. On this day there were two attacks of convulsive twitchings, the more severe one involving the entire body and lasting for two minutes. There were similar seizures on the ninth and tenth days. On the ninth day 2 grains of calcium bromide were given every six hours, and a dram of 25 per cent magnesium sulphate solution every four hours, the diagnosis now having been changed to convulsions because of cerebral edema. Loss

of edema and of weight (Fig. 2) began on this day, the ninth day. There were four to six watery stools daily. On the twelfth day the magnesium sulphate was stopped, the stools became more solid, the amounts of urine voided increased, and the loss of weight continued. The urine was negative throughout. By the fourteenth day all edema had disappeared, and the infant appeared entirely normal. Blood chemistry study on the eleventh day showed nonprotein nitrogen, 29.2; total protein, 4.5 (albumin 2.6 and globulin 1.9). Since his discharge from the hospital the infant has been seen several times and is above average in his physical and mental development.

In seeking for an explanation of these two cases of edema, our first thoughts had been of some disturbance of kidney excretion. But the negative, or practically negative, urine examinations and the blood chemistry findings in both cases were contrary to such a supposition. Their occurrence, when the infants were fed a hydrating type of solution and the recession of edema upon reduction of their consumption of this solution made it seem probable that the edema was a result of the feeding. This suspicion was strengthened by a review of the types of weight gains common to practically all of the infants that were fed this solution. Such phenomenal gains could scarcely have been explained except by unusual water retention.

The question then arose as to which element or combination of elements in this solution was responsible. In this solution, as given, there was 5 per cent dextrimaltose, 0.1 per cent sodium chloride (that is, 5 per cent of the 2 per cent sodium chloride present in the dextrimaltose powder) and 0.5 per cent sodium citrate. We decided on an elimination method for detecting the edema-causing element. Successive series of infants (thirty infants in each series) were then placed on various combinations of the above.

Other sugars were used also, and comparisons made with them. The number of infants in each group is, of course, too small for statistical accuracy but is large enough for our purposes, particularly since the differences between various groups were striking enough to be significant for our comparisons.

The average amounts of prelacteal feeding taken by all the groups were:

1st day— 5 oz., or 4.16% of birth weight,
2nd day—11 oz., or 9.16% of birth weight,
3rd day—11 oz., or 9.16% of birth weight,
4th day— 8 oz., or 6.66% of birth weight,
5th day— 6 oz., or 5.00% of birth weight,
6th day— 5 oz., or 4.16% of birth weight,
7th, 8th, and 9th days—3 oz. (2.5%) each day.

These amounts were very nearly the same in each of the groups.

Intradermal salt solution skin tests were done of the infants of several groups without significant findings of abnormal affinity of the tissues for water.

In Table I are given the comparative weight gains and losses in the different groups of infants. Several points are immediately evident. All of the groups of infants getting dextrimaltose showed proportionately less initial weight loss and earlier regain of birth weight than corresponding groups getting other sugars. This was especially evident when a hydrating agent (sodium citrate) was added. These groups also illustrate the hydrating quality of sodium citrate. They also show the extra hydrating quality of dextrimaltose No. 1, which can be due only to the sodium chloride, the only difference between dextrimaltose No. 1 and No. 2, the former having 2 per cent sodium chloride added to the dry sugar. This makes a 1:1,000 concentration of sodium chloride in the 5 per cent solution. But Group 8, in which the feeding contained both the sodium chloride and the sodium citrate, still does not show as much evidence of hydration as Group 7.

TABLE I

COMPARATIVE WEIGHTS OF GROUPS ON VARIOUS PRELACTEAL FEEDINGS (THE FIGURES REPRESENT THE AVERAGES FOR THE 30 INFANTS OF EACH GROUP)

	FEEDING GROUP	BIRTH WT. LB.	BIRTH WT. OZ.	INITIAL LOSS	DAY BIRTH WT. REGAINED	OUNCES OVER OR UNDER BIRTH WT. ON EIGHTH DAY
1	5% beta lactose	7	8	7.38 oz. (6.13%)		−1
2	5% dextrimalt No. 2	7	5	6.14 oz. (5.24%)	9th	−1
3	5% dextrimalt No. 1	7	3	4.63 oz. (3.99%)	6th	+3
4	5% lactose with sodium citrate*	7	10	6.40 oz. (5.22%)		−1
5	5% beta lactose	7	8	5.15 oz. (4.26%)	6th	+1
6	5% dextrimalt No. 2 with sodium citrate*	7	9	3.41 oz. (2.83%)	6th	+3
7	5% dextrimalt No. 1	7	10	3.83 oz. (3.16%)	4th	+3
8	5% beta lactose with sodium citrate* with 0.1% NaCl†	7	13	5.03 oz. (4.00%)	6th	+3

*The sodium citrate in each case was 0.5 per cent.

†The same amount of sodium chloride as is in a 5 per cent solution of dextrimaltose No. 1.

Dextrimaltose apparently is more hydrating than other sugars or at least enhances the hydrating qualities of added salts.

The graph of the selected group of six infants in comparison with another group (Fig. 3) shows one of the significant differences between the several groups that is not so evident in the total group weight charts. In every group except two, the weight curves were quite uniform, each of the individuals of the group following fairly closely the curve that represents the entire group. In the dextrimaltose No. 1 and sodium citrate group there was a considerable number (6 infants out of this group of 30, and 5 more out of another

group of 10) whose weight curves were like those of the infants with the edema, monsters, as it were, and there was evidence of excessive water retention. A few such weight curves occurred in the dextrimaltose No. 2 plus sodium citrate group. As was shown, they (like the infants with edema) gain sharply and then stop abruptly and even lose weight when breast feeding commences and automatically less hydrating solution is taken.

Nine additional infants were put on the dextrimaltose No. 1—sodium citrate solution subsequent to our other series in order that some blood chloride determinations could be made. Two of this group developed edema. Baby G., on the fourth day, gained 6 ounces but showed no

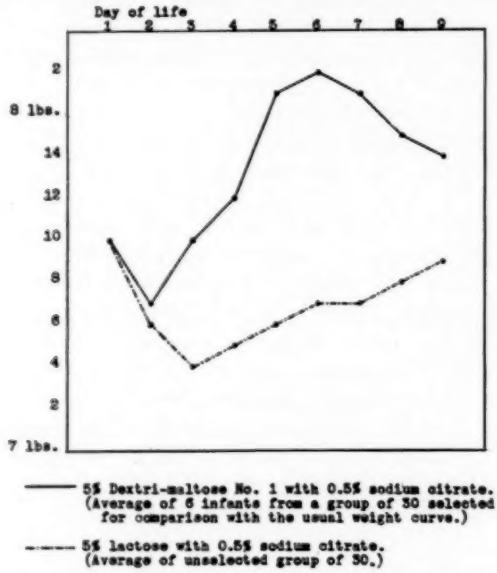
Day of life
1 2 3 4 5 6 7 8 9
2
8 lbs.
14
12
10
8
6
4
2
7 lbs.
5% Dextri-maltose No. 1 with 0.5% sodium citrate. (Average of 6 infants from a group of 30 selected for comparison with the usual weight curve.)
5% lactose with 0.5% sodium citrate. (Average of unselected group of 30.)

Fig. 3.—Weight curves of two groups of infants.

edema. Blood proteins and chlorides were determined. Two days later he was moderately edematous, and his blood proteins and chlorides were again determined. Neither before nor during the edema were the proteins or chlorides increased. During the edema they were decreased. Baby D. developed edema on the fifth day. The blood protein at that time was normal; the chlorides were decreased.

TABLE II

	PROTEIN	CHLORIDES
Baby G preedema	4.95	0.371
Baby G edema	3.9	0.363
Baby D edema	4.45	0.322
Normal newborn infants	4.5 to 4.56	0.392 to 0.43

On the three separate occasions on which we used the dextrimaltose No. 1—sodium citrate solution, one or more infants became edematous, a condition which had never occurred with any of the other sugars with or without sodium citrate, nor did it occur in Group 8 to whose 5 per cent sugar, sodium citrate and 0.1 per cent sodium chloride were added to make it comparable in every way with Group 7.

COMMENT

It is evident that no one factor of the edema-producing solution is entirely responsible. It was the fortuitous combination of three hydrating factors—the sugar, the sodium chloride, and the sodium citrate—that served to upset the delicate balance of the water metabolism of the infants. It was thought at first that the sodium chloride present in dextrimaltose No. 1 caused the edema, although it seemed unreasonable that a total of 1¾ grams of salt given over a period of five days could cause edema, as for example in Baby M. Yet apparently it was sufficient in the presence of the other two factors to overbalance the water-retaining mechanism. In the absence of either the sodium chloride (as in Group 6) or the sodium citrate (as in Group 3) no edema occurred, although in the former group there were some pathologic weight curves like those of the edema cases. In the group on dextrimaltose No. 2 the weight gains are distinctly better than on the other sugars—evidence of the hydrating quality of dextrimaltose alone.

One other investigator, Senn,[2] has already noted the danger of edema from a hydrating feeding, the gelatin solution recommended by Kugelmass. In two cases of sixteen of the series showing 650 and 661 mg. per 100 c.c., respectively, the mechanism apparently was one of sodium chloride retention causing the edema.

SUMMARY AND CONCLUSIONS

1. Four cases of edema in the newborn are reported. The edema was produced by a prelacteal feeding of 5 per cent dextrimaltose No. 1 to which 0.5 per cent sodium citrate had been added.

2. Dextrimaltose No. 1, dextrimaltose No. 2, lactose, and beta lactose were successively used in groups of infants to determine possible differences in weight gains on the different sugars.

3. The groups receiving dextrimaltose No. 2 or No. 1 (without added citrate in either case) gained as well as those on the "hydrating" solutions of 5 per cent lactose (or beta lactose) to which 0.5 per cent sodium citrate had been added.

We wish to thank Miss Cooley, head of the obstetrical nursing staff, for her cooperation in this work.

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INFLUENZAL MENINGITIS

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THE following communication records the results of a study of some clinical and bacteriologic observations on meningitis due to infection with *H. influenzae* and a discussion of the treatment of eleven patients who recovered. From January, 1919, until June, 1936, 106 cases of influenzal meningitis have been admitted to the Hospital for Sick Children.

Clinical Data.—An analysis of these 106 cases of influenzal meningitis is as follows: Seventy-eight per cent of the patients ranged in age from two months to three years, the youngest being seventeen days old, and the oldest ten years old. In a similar series reported upon by Fothergill and Wright,[4] they found that "80 per cent of the cases occur between the ages of two months and three years." Seventy of the patients in our series serve as an adequate control in the sense that lumbar puncture was the usual therapeutic procedure used. In this group of seventy there was only one recovery and sixty-nine deaths, a mortality rate of 98 per cent (Table I). The recovery of this child followed the use of an exsanguination transfusion. The remaining thirty-six cases received some form of "specific serum therapy." In this group there were ten recoveries and twenty-six deaths, or a mortality rate of 72 per cent (Table I). We feel that these results are of sufficient importance to justify a reference to our bacteriologic findings and a discussion of the treatment of the eleven patients who recovered (Table II).

TABLE I

YEAR	CASES	DEATHS	MORTALITY RATE
1919-1929	70 (untreated)	69	98%
1930-1936	36 (treated)	26	72%

Bacteriologic Data.—In 1910 Cohen and Fitzgerald[1] studied the characteristics of strains of influenza bacilli isolated in cases of meningitis. More recently this subject has been studied by Ward and Wright[2] and Pittman and Goodner.[7]

Since 1931 we have examined the cultural characteristics and serologic reactions of twenty-seven cerebrospinal fluid strains of *H. influenzae*. Twenty-five of these have been planted into sugar media con-

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TABLE II
SUMMARY OF CASES OF PATIENTS WHO RECOVERED FROM INFLUENZAL MENINGITIS

	PATIENT	AGE	SEX	YEAR	TREATMENT	ROUTE	COMPLICATION	RESULT	
1	C. B.	3 yr.	F	1924	Exsanguination transfusion			Cured	
2	B. T.	5½ yr.	M	1931	Transfusion, human serum only, continuous intravenous	I.T.* I.M.†		Cured.	Normal after 5 yr.
3	G. G.	11 mo.	M	1931	Anti-influenza horse serum and human serum	I.T.		Cured	
4	M. C.	20 mo.	F	1932	Bilateral craniotomy, anti-influenza horse serum and human serum	I.T.		Cured.	Normal 4 yr. later
5	S. C.	8 yr.	F	1933	Continuous intravenous, anti-influenza horse serum and human serum	I.V.‡ I.T. Cistern		Cured	
6	R. S.	6 yr.	M	1935	Continuous intravenous, anti-influenza horse serum and human serum	I.V. I.T.		Cured.	Normal 1 yr. later
7	W. H.	5 yr.	F	1935	Continuous intravenous, anti-influenza horse serum and human serum	I.T.	Deafness	Cured	
8	M. C.	5 yr.	F	1935	Continuous intravenous, anti-influenza horse serum and human serum	IV. I.T.		Cured.	Normal 1 yr. later
9	E. F.	2 yr.	F	1935	Continuous intravenous, anti-influenza horse serum and human serum	I.V. I.T.		Cured.	Normal 9 mo. later
10	G. R.	15 mo.	M	1936	Continuous intravenous, anti-influenza horse serum and guinea pig serum	I.V. I.T.		Cured.	Normal 4 mo. later
11	G. M.	2½ yr.	M	1936	Continuous intravenous, anti-influenza horse serum and guinea pig serum	I.T.		Cured.	Normal 3 mo. later

‡I.V., intravenous.
*I.T., intrathecal.
†I.M., intramuscular.

taining dextrose, maltose, and saccharose. Twenty of these strains produced acid in dextrose and maltose; the remaining five tested have not been uniform in this respect. All of the 27 strains have been agglutinated by polyvalent anti-influenza horse serum.*

Four recently isolated strains picked at random from the above strains have been found to be serologically identical in that they have reciprocally absorbed agglutinins from a rabbit serum prepared with each of the strains. The two strains recovered from the spinal fluid in Cases 10 and 11 (Table II) have been found to be similar in that they completely absorbed the agglutinins from the test serum.

Evidence of contact carriers harboring nasopharyngeal strains of the meningococcus serologically identical with the cerebrospinal fluid strain of the patient has been found by Silverthorne[8] in a number of instances in recent years. Interest was thus aroused in the carrier problem in the families of children with influenzal meningitis. In the family of a child suffering from influenzal meningitis, four contact carriers were obtained. Two of these nasopharyngeal strains were considered to be identical with the patient's spinal fluid strain in that they have reciprocally absorbed agglutinins from a rabbit serum prepared with each of these strains. This finding suggests that there is a "carrier state" similar to that known to occur in the contacts of patients with meningococcic meningitis. Further study of strains of *H. influenzae* from contacts is necessary before any conclusions may be drawn.

Treatment.—The method of specific serum therapy is outlined by Ward and Wright,[2] Ward and Fothergill[3] and Fothergill.[5] In this address[5] Fothergill reports nine recoveries from influenzal meningitis out of sixty patients treated with antiserum and complement, a mortality rate of 85 per cent. The above authors used two parts of antiserum to one part of complement in the treatment of their patients. Fothergill[6] has shown that there is an absence of complement in the spinal fluid of patients with influenzal meningitis. The effect of the antiserum is bactericidal, and the addition of fresh human complement is necessary for its action. In some of their cases[3] clinical improvement was coincident with sterilization and clearing of the cerebrospinal fluid. Some days later, however, their patients relapsed and died. At autopsy abscesses walled off from the general subarachnoid space were found.

In addition to the above method of treatment, we have introduced the use of the continuous intravenous injection of two parts of 5 per cent glucose and one part of normal saline in twenty-eight of the

*This serum was kindly furnished by Dr. LeRoy D. Fothergill, the Children's Hospital, Boston, Mass., and used in treatment of all cases with the exception of Cases 10 and 11 (Table II).

thirty-six cases. We believe that this may promote the flow of increased amounts of spinal fluid which flow facilitates more thorough drainage each time lumbar puncture is performed for the administration of serum. In all but one (B. T., Table II) of our "specifically treated" series, anti-influenza horse serum and fresh complement in a proportion of 7:3 have been injected daily, intrathecally. These injections have been given for several days after we have obtained repeated daily negative cultures of the spinal fluid. In sixteen out of thirty-six cases this mixture of serum has been given intravenously by the method outlined by Silverthorne.[9] By referring to Table II, one can see the results of the treatment.

During 1935 and the early part of 1936 freshly isolated cerebrospinal fluid strains have been obtained from infants and children with influenzal meningitis and preserved in a dry state under vacuum in second, third, and fourth subcultures. These strains have been used in the production of an anti-influenza *(H. influenzae)* horse serum. Guinea pigs were also injected with these strains, and their serum was found to develop bactericidal power similar to that produced in the blood of guinea pigs when vaccinated with the meningococcus.[10] It was shown by Ward and Wright[2] in the bactericidal test that fresh guinea pig serum is a more effective source of complement than fresh human serum. With these facts in mind, we administered in Cases 10 and 11 the mixture of anti-influenza horse serum and the bactericidal guinea pig serum intrathecally in the proportions mentioned above. One patient (Case 10) received the serum mixture intravenously. In this patient the spinal fluid remained positive (daily cultures) for approximately two weeks. Finally several negative cultures were obtained, and the child recovered and has remained in good health (a period of four months). In Case 11 the spinal fluid became sterile five days after the institution of treatment and remained sterile on repeated examination. This patient is also in good health four months after the illness. Some of our patients who recovered have been reexamined at later periods (Table II).

The strains recovered from the cerebrospinal fluid of these two patients were agglutinated by the above mentioned anti-influenza horse serum. The guinea pig serum which contained an average amount of complement was markedly bactericidal to both strains. Recovery of two successive cases treated by this method warrants its further trial.

SUMMARY

1. One hundred and six cases of influenzal meningitis have been admitted to the Hospital for Sick Children, Toronto, from January, 1919, until June, 1936.

2. From 1919 to 1929 there were 70 cases not "specifically treated with serum," with 69 deaths, a mortality rate of 98 per cent. The one patient who recovered received an exsanguination transfusion.

3. During the period 1930 to 1936, thirty-six cases were "specifically treated with serum," with twenty-six deaths, a mortality rate of 72 per cent.

4. Bacteriologic investigations are reported. Evidence is presented that the few cerebrospinal fluid strains tested form a homologous series. Two nasopharyngeal strains from contact carriers were found to be serologically identical with the cerebrospinal fluid strain of the case. This finding suggests a carrier state similar to that found in meningococcic meningitis.

5. An outline of eleven cases of patients who recovered is given.

6. The use of the continuous intravenous injection of glucose-saline solution with anti-influenza horse serum given intravenously is recommended. In addition, repeated daily intrathecal injections of the combined serums should be given until several sterile spinal fluid cultures are obtained.

7. A fresh bactericidal guinea pig serum combined with anti-influenza horse serum was used in the treatment of two patients in which recovery took place.

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SEVERE VISCERAL COMPLICATIONS IN ACUTE ANTERIOR POLIOMYELITIS

Case Report

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IN THE literature describing complications occurring in acute anterior poliomyelitis, there is a number of reports of visceral lesions occurring as the result of either toxemia or paralysis. There appears to be no record of the occurrence of hematuria and hypertension with death from renal damage following paralysis of the bladder complicated by pyelitis. In this instance these factors were accompanied by complete paralysis of the gastrointestinal tract with jejunitis and rectal prolapse, as well as the presence of lymphadenitis and further damage to other visceral organs. Greater interest arises here because of the violence of the onset causing prompt skeletal muscle paralysis, and the improvement clinically from the original poliomyelitis, with, however, sudden death as the result of an intercurrent visceral lesion entirely apart from the central nervous system changes.

The following report includes only the salient features having a bearing on the visceral lesions produced during the course of the illness.

CASE REPORT

A boy, aged thirteen years, who had been active and well until after a mild three-day pharyngitis and vague abdominal pain with constipation, suddenly developed a loss of power in his lower extremities, and within a few hours was unable to use his trunk or shoulder muscles. Before eighteen hours from the beginning of weakness in the legs, he had an almost complete paralysis of neck, shoulders, arms, chest, trunk, and legs, and he was placed in a Drinker-Collins respirator.

The patient was first seen when admitted to the Bryn Mawr Hospital on Aug. 10, 1935, during approximately the fourteenth hour after the onset of paralysis. An immediate lumbar puncture partially relieved the moderate rigidity of neck and back. The spinal fluid was under 16 mg. of pressure, contained 163 white cells and a few red cells, and showed globulin two-plus, sugar one-plus, and Wassermann reaction negative. A cervical adenopathy which gradually receded but did not disappear was noted. Shortly after the first of four daily administrations of convalescent plasma (50 c.c. intravenously and 50 c.c. intramuscularly) and glucose (50 c.c. of 50 per cent solution intravenously), there seemed an arrest of extension of the inflammatory process upward, although there was a gradual further involvement of those muscle groups which had not been previously overwhelmed. On the fourth day after the onset of the paralysis there was a slight return of function in the accessory muscles of respiration, and, since the temperature had dropped gradually from 103° to 99° F., the convalescent serum was discontinued. From the first there was difficulty in voiding and inability to empty the rectum. A distention of the urinary bladder and of the abdomen as a whole was a natural consequence.

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Bowel.—There was complete paralysis of the bowel, with absence of peristaltic auscultatory sounds and complete flaccidity of the rectum and anus with prolapse from the first to seventh day. There was a gradual return of function thereafter.

Nausea.—Nausea and vomiting occurred at irregular intervals throughout the illness.

Bladder.—Complete paralysis of the bladder and abdominal wall was present. The bladder was emptied by gentle manual pressure above and behind the overfull bladder. Catheterization was not performed.

Urinalyses.—Urinalyses showed albumin and white blood cells, occasionally granular cells and casts, and early in the illness a few traces of acetone. Specific gravity showed a low normal, varying between 1.010 to 1.003. Hematuria was first noted on the sixth day, again on the fourteenth day when there was pain in the penis, and again on the eighteenth and twenty-eighth days when there was pain in the renal areas and white cell count rose to 16,000.

Blood studies.—The serology was negative; chemistry variable with urea nitrogen 14 mg.; urea nonprotein nitrogen 40 mg.; and sugar 135 mg.

Hypertension.—The blood pressure was 150/110 continuously with the lowest reading at 130/110.

Paralysis.—During the first six days he was in the respirator, the paralysis of the respiratory muscles was so complete that it was necessary to force oxygen and carbon dioxide under pressure into the lungs and to press upon the abdomen and chest to expell it; this was done rhythmically in order to maintain life whenever it was necessary to open the tank or any of its windows to administer treatments or for nursing care.

On the seventh day there was a slight return in ability to use some of the accessory muscles of respiration, including a very slight return of diaphragmatic motion on the right side with some evidence of function in the pectorals. At this time a slight movement of the toes and fingers on the right side was perceptible. From this time forward there was a gradual return of strength in selected muscle groups. Muscles of the neck returned rapidly to nearly normal, and those of the upper right chest showed some increase in power. In the right arm there was a very slight return of power in the deltoid; the biceps responded weakly; and slight flexion and extension of the fingers could be obtained with ability to rotate the forearm slightly. In the left arm the deltoid showed no response, and the biceps showed a very slight return of contractability. There was no rotation of the forearm and no flexion or extension of the fingers beyond a barely perceptible motion. Neither lower extremity showed any return of power after the original gain of very limited flexion and extension of the toes.

It was possible to decrease gradually dependency on the respirator so that finally the patient could be moved away from the machine and out of doors for three hours a day with further increasing short intervals indoors. Return to the respirator was necessitated to avoid fatigue of recovering muscles of the chest, abdomen, and diaphragm. Intolerance to exercise was readily demonstrated by beginning of cyanosis and dyspnea, indicating the interval out of the tank was too long.

Mental.—The usual restlessness and apprehension at the onset in such cases was accompanied here by mild delirium for the first three days, and then there was a gradual return to active interest in surroundings, reading, and visitors. A mild state of anxiety existed throughout the illness, emphasized by the fact that the patient possessed an unusual intelligence.

Progress.—There was a steady, gradual clinical improvement in the condition of the patient except for the urinary findings, the persistence of the hypertension, recurring episodes of nausea, and the inability to accept adequate nourishment.

Terminal Event.—On the fifty-sixth day in the hospital, and after three days of gradually increasing nausea and restlessness, the patient again developed hematuria. During the early morning of the fifty-seventh day, dimness of vision developed, and

a twitching of the muscles of the face was noticed, first on the left side then on the right side. The head was pulled suddenly to the left and a generalized convulsion supervened, involving all the muscles capable of response. Consciousness was not regained, and a series of generalized convulsive episodes followed the first, with only a few moments between each. Pupils remained equal and reacted slightly to light during the brief intervals. At the moment of death, three and one-half hours after the first convulsion, there was a sudden change in the color of the face from deep cyanosis to extreme pallor.

Throughout the convulsive status the rhythm of the respirator could not be accommodated to the irregular spasms of the chest and forced administration of oxygen and carbon dioxide was extremely difficult. Intravenous luminal and glucose and lumbar puncture had made no impression on the severity of the episodes. Spinal fluid was under slight increase in pressure with three cells, globulin one-plus and sugar one-plus.

Postmortem Findings.—Summary of autopsy performed by Dr. Max M. Strumia, pathologist of the Bryn Mawr Hospital:

Thyroid: Grossly normal.

Heart: No pathologic lesions.

Lungs: Right lung, mild emphysema (apex). Left lung, atelectasis (base).

Liver: Bile retention, fatty infiltration.

Spleen: Follicular hyperplasia and amyloidosis.

Pancreas: Grossly normal.

Mesenteric Lymph Nodes: Severe follicular hyperplasia.

Intestines: Subacute jejunitis; hemorrhagic areas. Ileum showed no pathologic lesions.

Muscles: Atropic, degeneration and fibrosis.

Suprarenal Glands: No pathological lesions.

Urinary Bladder: Paralytically distended, with chronic cystitis.

Kidneys: Hydronephrosis. Acute ascending pyelonephritis. Hemorrhages in collecting tubules (possible source of hematuria). Pink staining and granular precipitation in capsular spaces and in tubules.

Cause of Death: Acute anterior poliomyelitis. Suppurative pyelitis with severe diffuse tubular nephritis.

Terminal Cause of Death: Hydronephrosis and pyelonephritis.

NOTE.—(A possibility that the convulsive episodes and terminal cause of death may have been due to a reactivation of the poliomyelitis infection involving vital centers was discussed, but could not be positively eliminated in the absence of postmortem examination of the central nervous system.

SUMMARY

During the course of an acute anterior poliomyelitis there occurred a sudden overwhelming somatic paralysis involving all extremities, neck, trunk, chest, and abdomen and a paralysis of intestine, rectum, and bladder. An early toxic nephrosis developed and quickly became complicated by an ascending infection, causing pyelitis. A severe tubular nephritis followed which may have been either secondary to the pyelitis or toxic in origin. The continued hematuria and hypertension with fatal termination several weeks after the acute phase of the poliomyelitis had subsided may suggest these findings as being of serious prognostic significance.

2025 WALNUT STREET

A SHIFT IN THE INFANT MORTALITY RATE IN DURHAM COUNTY, NORTH CAROLINA

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FOR the past five years, infant mortality has risen in many localities instead of falling gradually as it had during the preceding forty years. To ascertain, if possible, the causes of, and remedies for, this change, the following analysis was made of the death certificates of all infants under one year of age (including stillbirths) in Durham and Durham County from 1924 to 1935. They were divided into two groups: deaths which occurred in the first ten days of life, including stillbirths and deaths from prematurity even though they occurred after ten days of life (Table I); and those between the ages of ten days and one year (Table II). The usual division is between deaths under the age of one month and those between one month and one year. Since the number of deaths between the ages of ten days and one month were so few in this series, it can be compared with early deaths elsewhere.

For the entire twelve years syphilis appeared on only five death certificates for both colored and white races. Obviously the disease occurs much more frequently but, as Baker[1] has shown, it rarely is entered on a death certificate as a cause of death because it invalidates some insurance policies. Only ten diagnoses of tuberculosis were made in the years 1924 to 1935, probably for the same reason. In the tables they have been grouped with lung diseases and influenza and bronchitis under "pneumonia." "Intestinal diseases" include a multitude of causes, such as diarrhea, dysentery, colitis and obstruction (non-congenital).

The problem of the mortality in children over 10 days of age will not be discussed here, as it has been very adequately treated elsewhere and is more a matter of treatment and cure than of prevention.

As shown in Chart I, the total infant mortality rate in 1924 was 95.2 per 1,000 live births. This rate gradually fell to 71.1 in 1930, remained at that level until 1932 and then rose to 87.7 in 1935. From 1924 to 1930 the colored and white infant mortality rates both fell, but during the past three years the two have behaved differently. From 1933 to 1935 the rate for colored infants continued to fall (from 131.5 to 99.3), whereas the rate for white infants rose very sharply

From the Department of Pediatrics of Duke University School of Medicine, with the cooperation of the Durham City and County Health Departments.

TABLE I

DEATHS IN INFANTS IN FIRST TEN DAYS OF LIFE (INCLUDING STILLBIRTHS)

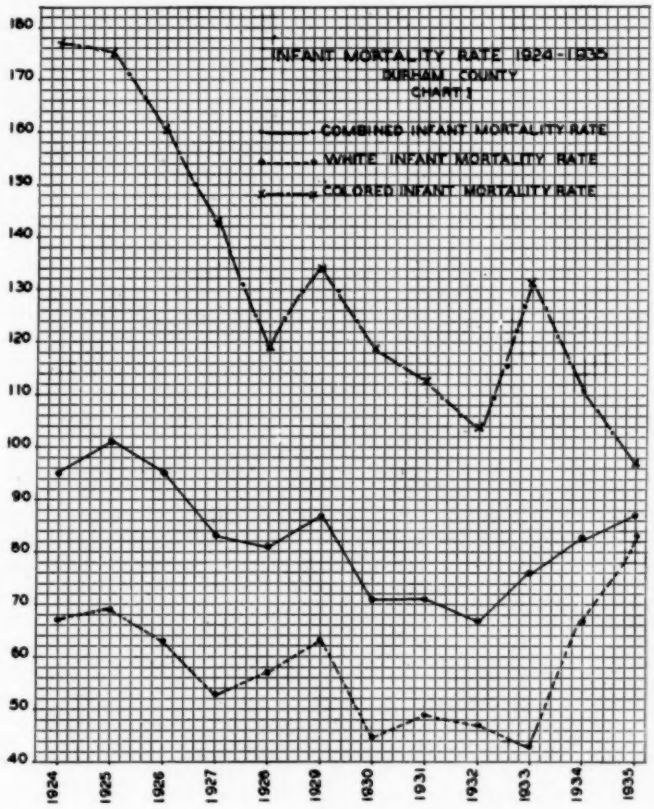
CAUSES	WHITE												COLORED											
	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935
Stillbirth	32	45	44	36	27	30	35	28	44	31	29	34	36	52	33	51	57	73	60	47	51	46	50	50
Prematurity	33	22	33	30	24	17	19	34	26	16	32	39	19	27	28	26	14	17	19	19	22	21	20	24
Accident	2	1	1	0	2	0	1	0	2	0	3	2	0	0	0	0	0	1	0	0	0	2	2	1
Pneumonia	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	2	0	0	0	1	0	1
Unknown	1	5	3	1	2	3	3	0	3	0	1	0	3	4	6	3	4	3	12	5	0	5	0	0
Congenital abnormalities	4	5	3	2	2	5	2	1	2	1	4	3	1	1	1	1	0	2	4	2	7	2	6	2
Malnutrition	1	0	1	0	1	0	0	0	0	0	0	0	0	2	0	0	0	0	1	0	0	0	2	0
Meningitis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Intestinal diseases	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	1	0	1	0	0	0	0
Status lymphaticus	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhagic disease of newborn	0	0	4	2	0	1	1	1	2	0	4	1	0	0	0	0	2	0	0	1	0	0	0	0
Icterus	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1
Tetanus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Totals under 10 days	73	79	89	71	58	56	63	67	80	49	74	79	59	88	67	85	77	99	96	76	81	77	80	79
Totals 10 days to 1 yr.	35	32	27	24	25	34	23	18	14	10	23	31	47	45	54	49	53	55	33	32	29	40	34	29
Totals under 1 yr.	106	111	116	95	83	90	86	85	94	59	97	110	106	133	121	134	130	154	129	108	110	117	114	108

Table II

Deaths in Infants From Ten Days to One Year Old

Causes	White												Colored											
	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935
Intestinal diseases	8	6	5	5	4	5	3	3	1	2	5	5	13	14	9	6	16	8	3	5	4	5	9	11
Unknown	5	5	7	3	3	2	5	1	1	1	0	0	13	7	14	8	13	16	8	10	5	4	6	4
Pneumonia	12	11	5	6	7	10	4	9	5	1	12	9	9	11	16	20	13	16	7	6	10	13	9	4
Croup	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	1	1	0	0	0	0
Malnutrition	2	1	0	0	2	2	3	0	1	1	1	1	4	5	2	4	4	10	9	2	3	12	3	4
Congenital abnormalities	3	5	1	1	2	2	2	2	2	2	3	5	1	1	2	2	2	2	4	0	3	1	0	1
Status lymphaticus	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	1	0
Icterus	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0
Hemorrhagic disease of newborn	0	0	2	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
Measles	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Accident	0	1	1	1	2	3	0	1	0	1	0	1	3	3	3	0	0	0	0	0	0	0	3	1
Pertussis	1	0	1	4	0	6	0	0	0	0	2	2	1	0	3	8	0	3	1	5	3	2	0	4
Meningitis	2	1	1	0	3	1	4	0	0	2	0	2	2	0	2	1	0	0	0	2	1	2	0	0
Malaria	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Retropharyngeal abscess	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Poliomyelitis	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Otitis media	0	1	1	2	1	0	0	0	2	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Renal	1	1	2	0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Diphtheria	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Convulsions (?)	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
Erysipelas	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tonsillitis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphatic leucemia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Totals	35	32	27	24	25	34	23	18	14	10	23	31	47	45	54	49	53	55	33	32	29	40	34	29

from 42.5 in 1933 to 83.2 in 1935. It is of interest that, although the birth rate for both races has been falling since 1924, during the past three years it has changed but little for both colored and white populations. Interestingly enough, as shown in Chart II and Table V, the combined infant mortality rates and stillbirth rates have followed a curve similar to that of Chart I. In the early years there was the same gradual fall for both races, but again the curve changes for the two



races from 1933 to 1935. In the colored race there is a continued decline, but in the white race there is a sharp rise.

As shown in Table III, of the total deaths under one year of age, the percentage which occurred during the first ten days of life (including stillbirths and deaths from prematurity) varied from 62 to 85 (average 74) in the white race, and in the colored from 54 to 74 (average 66). Most significant, however, as shown in Table IV, of all the deaths under ten days of age, prematurity and stillbirths accounted

for from 83-95 per cent (average 90 per cent) of the white deaths, and from 83-94 per cent (average 90 per cent) of the colored deaths. As deaths during the first ten days of life are usually due to prenatal causes, this difference between the white and colored figures seems to indicate a greater need for prenatal care among white mothers than among the colored.

TABLE III

PERCENTAGE OF INFANT DEATHS OVER AND UNDER THE AGES OF TEN DAYS

YEAR	WHITE			COLORED		
	UNDER TEN DAYS	OVER TEN DAYS	NO. CASES	UNDER TEN DAYS	OVER TEN DAYS	NO. CASES
1924	67	33	109	55	45	107
1925	72	28	111	67	33	133
1926	77	23	116	54	46	123
1927	75	25	95	64	36	134
1928	70	30	83	59	41	131
1929	62	38	90	65	35	154
1930	72	28	87	74	26	129
1931	79	21	85	71	29	108
1932	84	16	95	74	26	110
1933	83	17	59	66	34	117
1934	77	23	97	69	31	116
1935	72	28	110	72	28	110
Average	74	26		66	34	

TABLE IV

PERCENTAGE OF THE DEATHS UNDER THE AGE OF TEN DAYS WHICH WERE DUE TO STILLBIRTH OR PREMATURITY

YEAR	WHITE			COLORED		
	STILL. AND PREM.	MISC'L	NO. CASES	STILL. AND PREM.	MISC'L	NO. CASES
1924	89	11	73	94	6	59
1925	84	16	79	90	10	88
1926	89	11	89	91	9	67
1927	93	7	71	91	9	85
1928	88	12	58	92	8	77
1929	84	12	56	90	10	99
1930	86	14	63	83	17	96
1931	93	7	67	87	13	76
1932	87	13	80	91	9	81
1933	95	5	49	87	13	77
1934	83	17	74	87	13	80
1935	94	6	79	94	6	79
Average	90	10		90	10	

TABLE V

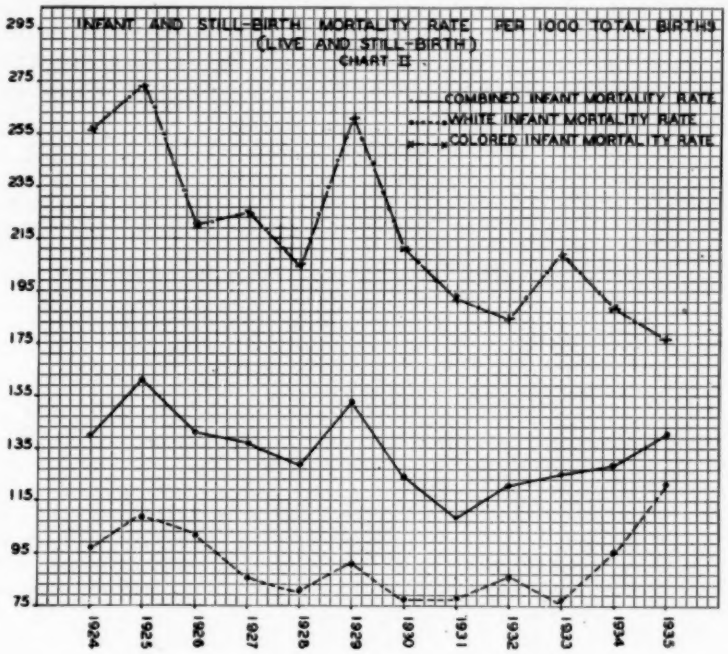
INFANT AND STILLBIRTH MORTALITY RATE PER 1,000 TOTAL BIRTHS (LIVE AND STILL)

	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935
White	96.9	109.3	101.9	86.2	81.8	91.1	76.8	78.0	86.5	76.0	99.6	120.9
Colored	258.8	271.7	222.4	225.6	204.4	260.8	213.3	194.3	184.0	207.0	190.2	175.7
Combined	140.0	161.5	141.2	135.5	128.6	151.6	126.5	110.7	121.0	123.8	130.6	141.0

The probable explanation for this difference in the figures for the white and the colored races is that during the depression years the

white mothers did not receive as much prenatal care as they had had previously, whereas the colored medical and obstetric care, which was predominantly midwife, was unchanged.

Gengenbach and his associates[2] in Denver, Colo., have shown that with proper prenatal and natal care the infant mortality was reduced from 178 per 1,000 live births to 15 per 1,000. Should not greater efforts be made to persuade expectant mothers, not only of the advisability, but of the necessity, of visiting their physicians at frequent intervals? The antenatal measures necessary for this reduction in infant mortality are simple and within the reach of any expectant mother



and are not beyond the resources of every competent physician.[3] The main difficulty is in establishing contact between the mother and physician. The infant and maternity program conducted in North Carolina by Dr. G. M. Cooper and the State Board of Health emphasizes this aspect of the problem by establishing prenatal clinics and urging expectant mothers to go frequently to their physicians.

The two remaining factors are the education of midwives and the improvement of environment. If midwives are necessary (they seem difficult to eradicate), they should be given short, comprehensive courses, concerning what a midwife should do and what she should not do. Periodic attendance at these courses, medical supervision, and

annual examinations should be compulsory in order to obtain and retain a midwife certificate. The living conditions of the "poor whites" and negroes in the South leave much to be desired but are beyond the scope of this paper.

SUMMARY

A shift has taken place in recent years in the infant mortality rate in Durham County, N. C. After a steady fall from 1924 to 1932, a rise has taken place from 1932 to 1935. An analysis shows that the rate for the negro population has continued to fall and that a sharp increase in the rate for white infants accounts for the rise in total rate. Further analysis shows this rise is chiefly due to an increase in the death rate of white infants in the first ten days of life. Lack of adequate prenatal care for white mothers is suggested as an explanation for this change.

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Critical Review

DIET THERAPY IN THE NEPHRITIDES AND IN DIABETES MELLITUS DURING CHILDHOOD

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AS AN adjunct to therapy, the patient's diet may act either as a supportive or as a corrective agent. Therapeutic alterations of diet may consist either in the proscribing of foodstuffs considered undesirable because of the nature of the patient's illness or in the prescribing of specific types of foods as therapeutic or nutritional agents. Much of the diet therapy of the past generation has been confined to the former objective; for a patient to "diet" implied that he was to be denied certain foods which his inclination would cause him ordinarily to use. With the discovery of specific diet deficiencies which lead to recognizable disease, the prescription of specific corrective foods or nutritional elements has become recognized as helpful in ameliorating or curing such disease. Nutritionists are offering us increasing evidence that in addition to the obvious "deficiency diseases," such as rickets, scurvy, beriberi, etc., many other states of suboptimal nutrition exist, which may manifest themselves as distinct disease, or which may merely prevent the attainment of optimal health. It becomes increasingly apparent that the quality and quantity of the diet play a large part in attaining and maintaining health. Much of the established knowledge in the field of nutrition has not yet become a part of the physician's armamentarium. Newburgh,[1] in commenting on this situation, has made the following statement: "In the absence of this new knowledge, the physician has accomplished little through diet because he centered his attention on the omission of foods. He is urged to acquaint himself with the quality and the quantity of the constituents of the normal diet. This is his only assurance that he will not prescribe for his patient a diet that is deficient in any respect. He must then decide whether the condition of the patient requires an increase or a decrease of any one or several of the dietary constituents so that he may modify the normal diet to meet the new requirements." In the same article Newburgh points out that the nutritional needs of the adult have been established more definitely than those of the child. As has been emphasized in earlier reviews in this series,[2] the needs of the child are distinctly more than an aliquot of those for the adult. Because of the requirements for growth, the child requires greater liberality of diet than does the mature individual; moreover, because of his lessened margin of safety, poor diets will lead to potential or outspoken disturbances of function or of structure much more readily than will similar degrees of relative deficiency in the adult. This distinction between the needs of the child and of the adult often is ignored by clinicians and by those who

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have written articles and texts pertaining to diet therapy. While nothing is to be gained by referring specifically to the standard texts which are deficient in this regard, it is necessary to call attention to the fact that with but few exceptions published material pertaining to diet therapy is directed toward the adult; often no mention is made as to the need of modifying the recommended regimen for the child, and, when mention is made of the child, frequently the recommendations are faulty or inadequate.

Discussion of therapeutic dietetics requires distinct consideration of the food needs of the patient as an individual as compared with the therapeutic indications for inclusion, limitation, substitution, or other modification imposed because of the disease. Of the two, the former considerations should receive the greater weight, and should not be compromised if in any way avoidable. Christian,[3] in discussing diet therapy in chronic nephritis, has emphasized this point: "We recognize that the disease is by no means limited to the kidney. Now practitioners are more influenced in their plan of treatment by consideration of the patient as a whole than in the past; now they consider less the dietary constituents that theoretically increase the work of the kidney and are more concerned with maintaining the nutrition of the patient at a high level. The use of a high caloric diet in prolonged fevers, such as typhoid, has taught the benefits and shown the absence of harm from such diets and has been an important influence in greatly liberalizing the dietary management of the nephritic patient of any type."

In the management of some diseases, our therapeutic approach is hampered because of ignorance as to the pathologic physiology involved in its causation. Often empirical therapy has been based on a misinterpretation of physical or laboratory signs. For example, when abnormality of the kidney or of the urinary constituents has been apparent, it has been rationalized that the kidney should be put at rest; that substances requiring elimination through the kidney should be withheld from the diet. This has served as the rationale for the limitation of protein foods, salt, and water in the treatment of albuminuria, edema, hematuria, or manifest renal disease of any type. The inefficacy of such therapy has been attested by the poor therapeutic results obtained by such measures in patients seriously ill with renal disease; the recovery of the milder cases has occurred in spite of, rather than because of, such limitations. The chronicity and many of the complications of renal disease, such as anemia, nutritional edema, and marked malnutrition, should be attributed as much to the nature of the therapy as to the underlying disease.

NEPHROSIS

Lipoid nephrosis (tubular or parenchymatous nephritis) is characterized by persistent albuminuria, intermittent edema often of marked degree, and an essentially chronic course. Frequently it is associated with transitory or continued evidence of glomerular nephritis as well. Many writers prefer the term "nephrotic syndrome" to "nephrosis," implying thereby a parenchymal disturbance which has led to edema. For years it has been known that the condition is associated with lowered content of serum protein, and this lowering was mentioned by Epstein[4] as an important causative factor in the disease. Recent

experimental work has established beyond doubt that lowering of serum protein will predispose the animal organism to the development of edema, and, if sufficiently low values are attained, its occurrence is predictable.[5] The prolonged and marked loss of albumin in the urine necessarily will deplete the body's supply of protein and seems sufficient explanation for the lowered values for serum protein observed in patients with nephrosis. If low protein diets are prescribed, as has been the custom of many therapists in the past, the regeneration of protein will be impaired and the condition will become worse rather than better. The recent reports of Dodd and Minot[6] offer evidence that hypoproteinemia occurs with surprising frequency in children who are receiving diets similar to those employed by the poor. Recurrent or chronic infections also impair protein synthesis and often lead to albuminuria. Thus two prevalent conditions—undernutrition and chronic infection—favor the development of hypoproteinemia and, if sufficiently effective, may induce edema and favor development of the nephrotic syndrome. Logical therapy will be directed toward measures which will aid in the restoration of serum protein; the diet should contain protein in amounts adequate to compensate for that being lost in the urine, to replenish the tissue deficit, and to permit normal synthesis. This requires the use of a diet high in protein. In the child it means relatively much more protein ingestion than in the adult. Under normal conditions, the daily requirement for the child is two to three times as great per unit of body weight as in the adult; a minimal safe allowance is a gram per pound per day. With nephrosis associated with considerable protein loss, the amount needed may exceed this considerably. Liu and Chu[7] have reported balance studies of patients with nephrosis, and their data indicate that for the adult an intake supplying per kilogram of body weight each day the equivalent of 60 calories, and 1.8 grams of protein, was optimal during nephrosis; with a thirteen-year-old boy, the need was proportionally greater than the usual childhood optimal level of intake.

There is greater unanimity of opinion as to the desirability of a high protein diet in nephrosis than there is as to the suitable intake of salt and of water. O'Hare[8] recommends a diet which is salt-poor and with limitation of fluid intake to 1,000 c.c. or less per day for the adult. Christian,[3] commenting on the treatment of edema in chronic renal disease, likewise states that with the use of diuretics there should be limitation of fluids in the diet and that a very low sodium chloride intake should be tried. Newburgh[1] takes an opposite view. He states that ". . . . it has been almost universally taught that blockage of the kidneys is the cause of nephritic edema. According to that doctrine, to get rid of the edema one must remove the water by other routes and at the same time one must permit as little water as possible to enter the body. Only a few simple experiments were needed to show the utter fallacy of these earlier beliefs and to indicate the shocking amount of harm that their acceptance has worked. Examination [of data] shows that the kidneys of the edematous subject were able to secrete a very large amount of urine containing a normal amount of solids as soon as he was permitted to drink a sufficient amount of water." According to the present concept, the retention of water in the tissues of those with noncirculatory edema is dependent on colloidal imbalance in the tissues and body fluids, and the condi-

tion is remediable only through measures which will permit reestablishment of normal fluid interchange. The evidence for the innocuousness or desirability of unlimited water intake in nephrosis is more convincing than that for sodium chloride.

NEPHRITIS

In acute nephritic states, characterized by the excretion of blood, one may consider the justification for dietary measures which would not be excusable as a continuous form of management in chronic disorders. Christian[3] states that "only in the early days of a very acute nephritis should diet be restricted in both amount and variety. For a week in such cases a diet of fruit juices and carbohydrates with restricted fluids is advisable. Then rapidly the diet should be expanded to one essentially adequate in amount and variety with only moderate restriction of protein, salt, and fluid, a diet not very different actually from a normal diet, free from any excesses." Some practitioners recommend that the treatment of acute hemorrhagic nephritis utilize occasional "sugar days," when the intake consists solely of well-sweetened fruit juices and of water. Such a regimen seems effective in shortening the duration of the period of hematuria.

Possibly the most revolutionary change of view in diet therapy in the treatment of nephritis is the liberalizing of the diet for the patient with chronic nephritis with evidences of chronic renal insufficiency. Here, if anywhere, one might feel justified in directing his attention primarily to the functional capacity of the kidney and decide that rigid diet restrictions were imperative. However, several leaders in this field of therapy recently have expressed the fallacy of unwise restrictions in even those patients showing marked functional impairment. Christian[3] states, "Chronic nephritis of all sorts is first of all a chronic disease. This means a long period of management and necessitates a continued entirely adequate diet, adequate both as to food constituents and as to the caloric requirement for the activity allowed to the patient." O'Hare[8] states similarly, "First and foremost [in the treatment of chronic nephritis] is the maintenance of the health of the whole body. . . . Finally it means a diet constructed to avoid undue strain on the kidneys by all products of excretion." He comments on the harm which will result from over-restriction of protein, since such limitation in itself may handicap the organism and lead to the destruction of body protein. As renal function fails progressively, he recommends that the fluid intake be correspondingly increased. Newburgh states, "In advanced stages of chronic nephritis it may take three times the normal amount of water to remove each gram of urinary solid. Under these circumstances the minimum intake that will prevent retention and dehydration is 2,500 grams of water a day."

Aldrich and Boyle[9] have recorded most interesting observations in the treatment of children with chronic nephritis. The report is concerned with forty children who at some time in their nephritic course had presented edema, arterial hypertension, increase of blood nonprotein nitrogen, hematuria, marked albuminuria, cylindruria, and a rapidly fatal or a chronic course; they represent a form of disease which is most unsatisfactory to treat, and which offers in general a decidedly poor prognosis. They state that while treating such patients with a low protein diet they had never seen the disease brought to a

complete standstill, the patients remaining chronic invalids. Up to the fall of 1930 such a regimen, with salt restriction, had been uniformly employed, and in spite of such therapy the children were remaining chronically ill and were dying. At that time a marked departure from former therapeutic measures and philosophy was inaugurated; all efforts were to be directed toward the improvement of the physical and mental hygiene of the child as a whole rather than directing treatment toward the renal condition. This was felt justifiable since many of the findings of the patients under the earlier management had suggested abnormalities of nutrition or of hygiene, the earlier treatment had been futile if not harmful, and it was determined at least to make the remaining life of the patients happy and comfortable. Under the new plan, each child received a diet designed to meet any deficiency. Meat or eggs were given at each meal; salt was not limited except in those definitely edematous; each received all recognized vitamins through the intake of cod liver oil, yeast, orange juice and raw and cooked vegetables. Other measures were taken to improve the general hygiene and to promote comfort and happiness. Favorable results were rapidly noticeable. Not only did the children appear better, but there also was decline in symptoms, blood pressure, albuminuria, blood nonprotein nitrogen, casts, and degree of anemia. Some of the patients died, but as a whole the results were definitely superior to the earlier regimen. They conclude that on the basis of two years of such therapy, the majority of their patients have shown definite clinical improvement, three have shown complete disappearance of clinical evidences of the disease, one is continuing his downward course but at a retarded rate, and the death rate has been decidedly reduced.

DIABETES MELLITUS

The prognosis in diabetes mellitus is most intimately dependent on the type of management employed. With no control, the life of the child with diabetes mellitus usually can be measured in months. With mediocre management, it is easy to keep the diabetic child alive and to reconcile one's self to the inevitability of the serious or fatal complications and sequelae which come to the patient so treated. With the use of the measures now available to the diabetic child, one can offer a prognosis as to life, freedom from complications, and vigor of health on terms practically as favorable as for the well-cared-for normal child, providing full use is made of such therapy by the physician and the patient. No halfway measures of adequacy of treatment may justifiably be considered in comparing various regimens of therapy.

The objective, then, in the dietary management of diabetes in the child is to approximate ideal conditions so far as possible; merely to hold the disease in check is not enough. Prior to the time when insulin became available, undernutrition offered the only recourse for controlling glycosuria. The idea that undernutrition is essentially related to the welfare of the patient with diabetes is hard to eradicate. Gray and Sansum[10] point out that one of the triumphs of insulin therapy is that it makes nutritionally adequate diets possible. Geyelin[11] comments on the persistence with which a large group of clinicians cling to the fallacious theory that undernutrition is the sine qua non of diabetic therapy. Most writers on the subject who comment on the

food needs of diabetic children admit that the diets should be physiologically adequate, providing for normal growth, development, and maturation. Many also refer to the desirability of adapting the regimen so as to simulate that of the normal child so far as possible. Out of this relative constancy of objective, various types of dietaries and standards for normality of diet have arisen.

The reviewer is inclined to ignore the reports of those suggesting free-choice diets for children with diabetes, agreeing with Grote[12] that the free-choice diet is not a therapeutic diet in the true sense of the word and that its use undoubtedly deprives us of one of the most important means of combating coma. A self-choice diet will be no better in its general nutritional characteristics than the diets of nondiabetic children living under similar conditions. We have plenty of evidence that the use of a self-choice dietary regimen, unless conditioned by a director who has insight into the food requirements for normal nutrition, will result in an inferior type of diet. This view has been emphasized in earlier reviews of this series. The following quotation, taken from the report of the Mixed Committee of the League of Nations, "The Problem of Nutrition," offers further opinion concerning this point:[13]

"Over large areas of both agricultural and industrial countries are to be found distressed groups of population, especially where the incidence of the depression has been most severe. This is true even in such well-to-do countries as the United States of America and the United Kingdom. Defective nutrition among wide sections of the population is not, however, limited to countries or areas especially affected by the economic crisis, such as impoverished urban communities or depressed agricultural areas. In the light of modern knowledge, it is abundantly clear that in no country does the whole population attain the standard scientifically desirable in the interests of health. . . . defective nutrition is to be found among large sections of the population even in well-to-do countries, with the inevitable consequence of the prevalence of deficiency and the unsatisfactory standard of physique of the population as a whole. . . . in the United States of America it was thought until recently that the standard of life was high, especially having regard to the consumption of milk and other protective foods. Nevertheless, recent enquiries by scientific workers have shown that a number of persons are insufficiently fed and a much larger number badly fed. Even in 1928 and 1929, which was a period of great prosperity, most families were living on inadequate diets. Since the economic depression, the position has become worse . . . it thus appears that, in the United Kingdom, the diet of at least 50 per cent of the population falls short of the desirable standard; and it is estimated that to raise the consumption of this low-income half of the population merely to the level of the next group would require an increase of 16 per cent in the amount of milk consumed, 15 per cent in that of butter, 18 per cent in eggs, 12 per cent in meat, as well as a 25 per cent increase of expenditure on fruits and vegetables. Even then the diet would leave room for considerable improvement. The analysis of family budgets carried out by the International Labour Office . . . demonstrates the existence of similar conditions in other countries."

In a further statement, this fault in prevalent diet habits is attributed to lack of knowledge concerning proper nutrition. "Ignorance (re nutrition) is prevalent, not only among the poorer classes of the population, where it aggravates the ill consequences of lack of resources; investigations made in the wealthiest countries have revealed the fact that defective, inadequate or ill-considered nutrition exists, and that even among the wealthier classes there is ill-considered nutrition due to inadequate knowledge."

The question might be raised as to whether there is reason to believe that the food requirements of the diabetic child differ in any essential from those of the normal child. A review of available data offers no evidence that such differences exist. Further, one must determine whether there is anything in the diabetic state which mitigates against using a normal diet for the nutrition of the diabetic child. If the physiologic economy of such a child is peculiar, then the diet should be adapted so as to compensate for it. Priesel and Wagner[14] speak of the dilemma presented by the diabetic child, who needs calories as the normal child, but who because of his diabetes needs to restrict his calories. Apparently this need for restriction is determined by economic factors which limit the availability of insulin. If the insulin dosage need not be limited, the calories may be kept at as high a level as is desired. It seems true that the efficacy of insulin is greatest when the diet is limited;[15] unit for unit, more effect is seen from insulin given the underfed patient than one who is more amply fed. This hardly establishes the need for limiting the caloric intake of such children, however. The amount of insulin which may be used offers an economic problem, not one of physiology. While economic conditions may make it necessary to compromise between the needs of the patient and his ability to provide for them, such compromise should be the exception rather than the rule. If it is possible to give the diabetic child as favorable a diet as the nondiabetic child, this should be done. As is expressed in the League of Nations report referred to above, we should work toward "the adoption, not of the indispensable minimum, but of the optimum diet as the standard."

The League of Nations report on the physiological bases of nutrition[16] offers desirable standards of caloric intake for normal children, ranging from 840 calories for children up to two years of age to 2,400 calories for children over twelve years; these allowances are to be supplemented to meet the degree of activity of the child. Most of the diets described by clinicians treating children with diabetes fall considerably short of these norms. White[17] recognizes this deficit, stating that her diets nearly equal the requirements of the quiet child as described by Lusk. She expects the diabetic child to be relatively inactive and adapts the diet accordingly. Priesel and Wagner[14] offer diets which appear to be considerably more liberal, but which still fall below Pirquet's standards for normal children. Geyelin[11] advocates the use of diets which are normal in calories.

In determining the caloric allowance for the child, various methods are employed. The prescribing of calories according to body weight seems prevalent. White[17] offers 90 to 100 calories per kilogram of body weight up to a year, 75 calories up to five years, 50 to 75 calories up to ten years, 40 to 50 calories from ten to fifteen years. Gray and Sansum[10] offer from 45 to 80 calories per kilogram, dependent on the

child's age. Basing the diet prescription on the child's weight is satisfactory if the child weighs the amount that a normal child of the same height or age should weigh. If the child is underweight, overweight or retarded in height, such a gauge for the adequacy of the diet will tend to perpetuate the child's abnormal state. It seems much wiser to base diet requirements on the child's height rather than weight and, moreover, to exceed the calculated allowance when the child is underheight for his age. Earlier data on the growth of diabetic children led to the impression that such children do not grow normally; more recent data indicate that the normality of growth of the diabetic child is determined in largest measure by the adequacy of his food intake.[18] Priesel and Wagner[14] use a variant of the Pirquet system of nutrition, basing the child's needs on his sitting height. The reviewer has used the total height as a basis, and found it to be very satisfactory.[19]

There is fair unanimity as to the amount of protein needed by the normal child and the amount which should be assured by the diabetic diet. The normal optimum as stated by the League Committee is in accordance with figures generally accepted by nutritionists, ranging from a daily intake per kilogram of body weight of 3.5 grams for the child under three years to 2.5 grams for the child up to the age of fifteen. White[17] offers from 10 to 20 per cent of the calories as protein; Priesel and Wagner[20] formerly employed similar amounts, but recently have advocated the high protein intake used by Porges and Adlersberg; the amounts are not stated in terms of body weight or total intake, but definitely are greater than the usually accepted lower limits of desirability. Freise and Jahr,[21] on the other hand, use diets much lower in protein than the level which is considered essential for normal development.

The past decade has seen a marked tendency to liberalization of the diabetic diet as to its content of carbohydrate. This has been done so as to make the diet more palatable, less likely to produce ketosis, and more similar to the diet of the average child. Geyelin[11] states that the objective of most clinicians is to make the diet of the diabetic patient approximate that of the normal person. Working toward that objective, various ratios of carbohydrate to fat have been employed, sometimes as high as 3 or 4 to 1. Published and unpublished data seem to substantiate the statement that the total insulin requirement is proportional to the total calories ingested, not to the potential dextrose content of the food. Some observers feel that such diets require the use of less insulin than diets of equal caloric value but high in fat. Many are very enthusiastic about the advantages of such diets. Geyelin[11] states that "as the result of my experience during the past ten years with diets high in carbohydrate and normal in calories, I have been convinced that this is the treatment of choice, and that the diabetic patient so treated enjoys better health with no observable detriment to the fundamental state of his diabetes." Gray and Sansum[10] state that it is possible, practicable, and advantageous to feed the diabetic patient with a diet approaching a normal carbohydrate-to-fat ratio. In mild cases they have had satisfactory results with ratios of dextrose to fatty acid as high as 4 to 1, but this has not been true with more severe cases. White[17] uses a diet of intermediate carbohydrate content. Priesel and Wagner[20] have recently reported their

enthusiasm for the high carbohydrate, high protein, low fat diet of Porges and Adlersberg; however they state that one gets good results and occasionally poor results with either the high fat or the high carbohydrate dietary; they comment on the fallacy of expressing premature conclusions concerning any type of management; spontaneous improvement is to be expected with the initiation of any enforced system of management. Joslin[22] reports less stability in patients receiving high carbohydrate diets.

From the foregoing it may be fairly concluded that the proper control of diabetes mellitus in children is compatible with the use of diets high in calories and with a wide variety of levels of potential dextrose. The type of diet formula employed, then, should be determined not in terms of the management of the diabetes, but in terms of the nutritional welfare of the normal child. It has been stated that the objective of modern diabetic management is to approximate the regimen of the normal individual so far as possible. Before applying this principle too literally, we should make sure that the usual regimen of the supposedly normal child is a desirable one: we should not use his diet as a model if it is not a suitable diet for optimum health. Numerous authorities have pointed out the inadequacies of present dietaries, as has been cited in the foregoing. Dietary adequacy is measured quantitatively in terms of energy content and qualitatively in terms of the nature and amount of the protective substances it contains. The proportion of sugar-formers to fatty acids need not be considered from the qualitative standpoint, as long as the diet is not so predominantly high in fat that ketosis is imminent; this danger is avoided if the ratio of fatty acid to dextrose does not exceed 1 to 1, and higher fat intake may be employed with safety if occasion requires. An outstanding objection to the prevalent dietary for normal children and adults is the preponderant use of starches and other concentrated sources of sugar, with a resultant crowding out from the diet of the foods which carry more protective substances. From the nutritional standpoint, the optimum diet will be one offering at least half of the calories in the form of the protective foods. Such a diet will offer from 35 to 50 per cent of the total calories in the form of fats, 15 to 20 per cent in the form of biologically valuable protein and the remainder as carbohydrates; the latter should come predominantly from vegetables, fruits, and whole grain cereal products.

Thus the chief concern of the dietary therapist in treating the child with diabetes should be to prescribe a diet which is constant and predictable in its content of total calories, which is suitably proportioned among the various meals of the day, and which nutritionally is complete as to its content of protein, minerals and vitamins. In constructing the child patient's diet, it is most desirable to base the diet on the intake of a suitable amount of milk—approximately a quart per day per child. Cream and cheese can be used to meet this requirement partially; it is not readily practicable to construct an adequate diet without the use of considerable amounts of milk. "Milk is the nearest approach we possess to a perfect and complete food, and no other single food is known that can be used as a substitute."[16] In feeding the normal child, the League of Nations Committee recommended that milk supply from 100 per cent to 75 per cent of the total calories during the first year of life, about 50 per cent at three to five

years, and, through addition of other foods, declining relatively to about 25 per cent at adolescence. This is roughly equivalent to the maintained use of about a quart of milk a day throughout all of childhood. From the standpoint of economy, it should be remembered that skimmed milk may be safely used as the sole form of milk, if suitable supplements of other fats and of the fat-soluble vitamins are employed. Evaporated milk similarly may replace fresh milk. Eggs and meat should be used freely. Through the liberal use of a wide variety of vegetables and fruits—raw, fresh and canned or dried—the mineral and vitamin requirements will be met with the exception of vitamin D. The League Committee states that adequate provision of the vitamins other than vitamin D can be readily accomplished by inclusion in the diet of optimum amounts of such protective foods. It emphasizes the need for provision of extra vitamin D, wherever and whenever sunshine is not abundant. The indiscriminate use of irradiated foods, except in the case of milk, is deprecated.[16] When it is commercially available, the use of milk reinforced through the addition of vitamin D should be considered a desirable measure, and a necessary one if cod liver oil or equally potent source of vitamin D cannot be supplied daily throughout childhood.

Many unjustifiable fetishes have been associated with the dietary management of diabetes mellitus. One of these was the use of special so-called "diabetic foods." Such foods are supposedly low in carbohydrate, and as such were considered permissible or advantageous in the management of the disease. With the recognition that protein foods may supply as much as 80 per cent of their weight in dextrose, and that the insulin requirement is based on the total caloric intake rather than the amount of potential dextrose ingested, the use of these special foods becomes pointless. Many in fact are really concentrated forms of carbohydrate as compared with most vegetables and fruits. This is true of gluten flour products, dark breads, and other foods which sometimes are prescribed for these patients. The Council on Foods of the American Medical Association has recognized these facts in its refusal to sanction the advertising of foods as useful in the control of glycosuria if the content of potential dextrose exceeds 3.8 gm. per 100 c.c. of the product.[23] Marble[24] states that in the Deaconess Hospital (Boston) "of the so-called 'diabetic foods' almost no use is made. We consider the use of gluten bread, diabetic flour, and similar special preparations to be generally unnecessary and expensive adjuncts to treatment."

In view of the detailed knowledge needed pertaining to the chemical composition of food and to the distribution of the protective substances in foodstuffs, it is comforting to the physician that he can turn to tables of diets which have been calculated to meet the needs of the diabetic patient. However, unless he satisfies himself that such diets are prepared in accordance with the philosophy he adopts in diabetic management, he may handicap rather than help his patient through their use. Most of the published diets are designed for adults rather than children and are suboptimal in calories and protective foods even for the adult. Diet lists for children which have been widely distributed by one of the commercial pharmaceutical houses do not meet the standards of quantity or of biologic quality expressed in the foregoing as desirable. The diets which have been used by the reviewer in

the management of over two hundred children with diabetes mellitus are offered in *Brennemann's Practice of Pediatrics;*[19a] whereas minor changes have been made in these as now used in the Iowa Clinic, they will be found acceptable. The diet prescription is based on the child's height; the younger child or the one whose growth has been retarded because of earlier undernutrition is given separate consideration.

SUMMARY

In this and a preceding review of therapeutic dietetics[2d] emphasis is placed on the need for inclusion of protective foods in suitable variety and amount in all prescribed diets. Evidence has been offered to indicate that the diet of the average child cannot be considered as a suitable guide as to the food requirements during childhood. Recent literature reveals the tendency to liberalize therapeutic diets in the treatment of chronic diseases, attempting to approximate an ideal intake for a normal child so far as the nature of the disease will permit, and directing therapy more toward the welfare of the child as a whole than toward satisfying certain concepts of the pathology of his disease.

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American Academy of Pediatrics

Proceedings

SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MAY 11, 12, 1936

Round Table Discussion on Roentgenology of the Thorax in Children

The Monday morning session was called to order at 9:30 A.M. in the President Hotel, Kansas City, Mo., by Dr. Gerald M. Cline, Bloomington, Ill., and the Tuesday afternoon session by Dr. E. J. Barnett, Spokane, Wash.

Roentgenologic Consideration of Atelectasis and Other Manifestations of Bronchial Occlusion

L. R. Sante, M.D., St. Louis, Mo.

Regardless of the cause or manner in which it is brought about, bronchial occlusion produces the same results. Perhaps the most common cause of bronchial occlusion, especially in children, is aspiration of a foreign body. If the foreign body is composed of metal or other radiopaque material, its presence can be readily detected by roentgenographic examination; if it is of nonopaque material, then one must rely upon other manifestations of occlusion resulting from the occlusion for a diagnosis, not upon the detection of the foreign body itself. For a more satisfactory conception of the roentgenologic findings resulting from bronchial occlusion, a complete understanding of the attending physiologic process is essential.

Long before the discovery of x-rays Lichtheim, experimenting on rabbits and other animals, observed the sequence of events which followed complete obstruction of a bronchus by a bean. He noted that within a short time the portion of the lung supplied by the bronchus lost its air content and became atelectatic. That this was due to the absorption of the air entrapped in this portion of the lung by the circulating blood, was also proved by the fact that, when the circulation to the obstructed portion of the lung was also occluded, absorption of air did not take place and the lung did not become atelectatic.

When a lung loses its air content and becomes atelectatic, it becomes smaller in size by just a volume equivalent to the amount of air absorbed. The shrinkage of the lung exerts its effect on the entire pleural cavity: since there is no associated pneumothorax and the visceral and parietal pleurae remain in close apposition, the bony cage becomes narrower, and the ribs become closer together; the heart, trachea, and other mediastinal structures are drawn over to the involved side, and the diaphragm is elevated. It is by these fundamental characteristics that atelectasis is recognized in the roentgenogram. The atelectatic lung, being airless, is dense and homogenous—fully as dense as consolidation in lobar pneumonia.

Incomplete bronchial occlusion results in an entirely different succession of events. During inspiration the bronchi are slightly larger than during expiration; conse-

quently a foreign body lodged in a bronchus might be of just sufficient size to permit free inflow of air around it during inspiration and yet completely occlude the bronchus during expiration. The result would be that in place of atelectasis of the lung resulting from occlusion, there would be obstructive emphysema. Roentgenologically then, on inspiration both lungs appear well aerated and normal; on expiration the obstruction to the natural outflow of air is clearly seen because of the fully aerated lung and the immobile diaphragm and the chest wall on the affected side. Likewise, the increase in pressure on the affected side over the normal side results in the displacement of the mediastinal structures away from the involved lung during expiration and a return to normal during inspiration, producing a pendulum-like oscillation of the mediastinum back and forth during respiratory movement. Even if the foreign body is nonopaque, the existence of such findings is indication of its presence.

Many things may serve as occluding agents besides foreign body: tumors, bronchogenic or otherwise; congenital atresia and other anomalies; inspissated secretion, etc.

In addition to these forms of occlusions, there still remains a rather dramatic form of bronchial occlusion referred to as massive idiopathic atelectatic collapse of the lung. This occurs in children of all ages as well as in adults. It was first described by W. Pasteur in 1890 as an aftermath of diphtheritic paralysis of the diaphragm. Subsequently he called attention to its occurrence as a postoperative complication. During the World War, Sir John Rose Bradford again called attention to its connection with grave wounds under circumstances involving extreme exhaustion and high nervous tension. This has been described as a condition in which, "the lung, previously well aerated, without apparent cause, loses its air content and collapses." It occurs frequently following severe or even trivial injuries to the chest, abdomen, or pelvis or after operations, especially upon the abdomen, pelvis or rectum, regardless of type of anesthesia.

The exact cause is not known. The atelectasis which occurs undoubtedly is the natural sequence of bronchial occlusion by inspissated mucus; sometimes this is a thick gelatinous mucous plug, at others the lung is fairly "drowned" with thinner secretion. The part which still remains a mystery is the influence which results in abolishment of the cough reflex, permitting the collection of mucous secretion.

This type of involvement has been seen in debilitated infants and in those suffering from grave septic infection as a terminal manifestation.

It is possible, under fluoroscopic observation, to roll the patient *upon the unaffected side* and dislodge the obstructing secretion by forced coughing and thumping the patient upon the back; this manipulation in a great majority of cases results in immediate reinflation of the lung. The mere manipulation incident to getting a patient up into a wheel chair may be sufficient to cause partial or even complete reinflation; this serves to explain the discrepancy often found between the physical findings and the roentgen appearance of the chest.

MONDAY MORNING DISCUSSION (DR. CLINE PRESIDING)

DR. ROBERT BLESSING (EVANSTON, ILL.).—In support of the point Dr. Sante made, Dr. Porter Vincent, of Mayo Clinic, an internist who has turned bronchoscopist, criticized the practice of doctors in the matter of postoperative care, pointing out that neglect of proper care is a factor in the development of this condition. The surgeon is so interested in the prevention of discomfort to the patient and in the prevention of evisceration following an abdominal operation that he puts a huge abdominal binder on the patient's chest and soaks him with opiates, in an effort to prevent any cough reflex. The result is that the patient can scarcely

breathe at all. It would seem that the bronchoscopist would arrive at the same conclusion as Dr. Sante, that it is better to let the patient cough. His discomfort is not as bad as lung collapse or abscess from too severe immobilization.

DR. SANTE.—I can readily conceive how extreme postoperative immobilization may be a factor in production of atelectasis. There are many surgeons who use this method of rolling postoperative patients first on one side and then on the other, to prevent passive congestion, and the result has been a reduction in the number of these cases fortunately.

May I call attention to the use of carbon dioxide inhalation for hyperventilation after anesthesia for prevention of atelectasis. This has been effectual in preventing atelectasis in a large number of instances. Unquestionably the use of carbon dioxide is one factor which has reduced the number of these cases, and another is the fact that once a clinician sees it, he never misses it again. All he has to do is take the patient's clothes off and observe him closely. There is immobilization of the chest in lobar pneumonia, but in atelectasis there is not only immobilization, but the involved side of the chest is actually sunken. He rolls the patient on his unaffected side, and, if reinflation occurs, the patient is not brought to the radiologist.

DR. GEORGE H. GARRISON (Oklahoma City, Okla.).—At what age after birth does an infant completely expand both lungs?

DR. SANTE.—Complete aeration in the normal infant usually occurs immediately upon birth, within the first few minutes.

DR. GARRISON.—Do you think there is some collapse? Suppose you get plates some weeks after birth and they show an area of consolidation?

DR. SANTE.—If you see infiltration or any area of consolidation in the lungs of a newborn infant within a few days after birth, you may safely ascribe it to atelectasis, but ordinarily in a normal, healthy child complete expansion should be present.

TUESDAY AFTERNOON DISCUSSION (DR. BARNETT PRESIDING)

CHAIRMAN BARNETT.—How many patients with atelectasis develop bronchiectasis, particularly in the lower lobe?

DR. SANTE.—I suppose you refer to foreign bodies lodged for a long time in the lower lobes. Such conditions do result in bronchiectasis, but massive atelectasis is an acute process from complete occlusion of a bronchus and does not go on to bronchiectasis. The pull is not exerted on the alveolar structure or on the bronchi. It sometimes does result in abscess formation and necrosis. This is the danger of not taking care of such cases.

Of course, the high leucocyte count and high fever seen in such cases are due to the retention of secretions that would normally have an outlet from cough and expectoration.

DR. MORLEY D. McNEAL (Highland Park, Ill.).—Is it possible to have a partial collapse of a lobe, perhaps involving just a few small lobules?

DR. SANTE.—It certainly is, and it is sometimes very difficult, when you have just a partial collapse, to make the diagnosis.

You remember the illustration of the lateral view of the chest with a glass bead lodged in the bronchus. One could see hardly anything in the anterior view, but the

lateral view showed a triangular area of consolidation, the distribution of one of the smaller bronchi. The same process takes place no matter where the lodgment is, and no matter how large the bronchus is.

DR. ALBERT L. SALOMON (OKLAHOMA CITY, OKLA.).—The type of atelectasis to which you refer is fan-shaped in appearance, isn't it?

DR. SANTE.—It would be, because the distribution of the bronchus from that point out is naturally fan-shaped.

DR. SALOMON.—I recall this appearance of the x-ray film in the case of a child who had aspirated Johnson grass.

DR. SANTE.—It seems strange that it is possible to get physical signs in a lung which by definition is devoid of air; yet I am sure that transmitted breath sounds are heard. I think the physical signs one gets in lobar pneumonia are due to the same thing, transmission through solid tissue. Paradoxically, you should get "blowing breathing" in a lung that is devoid of air. Instead of vesicular breathing, you get blowing breathing. The blowing breathing through a larger bronchus is transmitted through the atelectatic lung.

DR. WALTER M. WHITAKER (QUINCY, ILL.).—In how many cases is bronchoscopic removal of the obstruction necessary for reinflation?

DR. SANTE.—All manner of anomalies have been found in the bronchi. Chevalier Jackson has found congenital atresia from membranes over the bronchus, with two or three little holes, the only means of passage of air, which undoubtedly had been there since birth. These may never give any trouble until a cold or local inflammation produces swelling and atelectasis results. It is obvious that in a case like that, you could stand the child on his head, or do almost anything, and his lung would not reinflate. Likewise, if atelectasis happens to be from bronchogenic tumor growing gradually until the bronchus is completely occluded, any amount of rolling or manipulation of the patient cannot be logically expected to remove the obstruction.

Roll the patient on his good side; don't treat him too gently; make him cough. It is a simple maneuver and very dramatic. If that maneuver does not work, that is, does not result in dislodgment of the offending mucus, go ahead with bronchoscopy.

DR. EDWARD D. ANDERSON (MINNEAPOLIS, MINN.).—In cases of atelectasis in the newborn, in which there is quite a mass of atelectasis, how long does it take to clear up if the child lives?

DR. SANTE.—That is a relatively rare occurrence in a healthy, full-term baby. It would be impossible to say how long because one never knows. It has occurred in premature infants and in feeble children who have been rather emaciated and do not breathe properly.

DR. LOUIS H. SEGAR (INDIANAPOLIS, IND.)—In "The Symposium on Sinusitis" it was said that autopsy reports showed 16 per cent, I believe, of deaths of newborn infants were due to atelectasis.

DR. HENRY G. PONCHER (EVANSTON, ILL.).—Do you consider atelectasis as a predisposing factor or forerunner of bronchial pneumonia? That is, is the patient more susceptible?

DR. SANTE.—When there is atelectatic lung that remains uninflated and uncared for, for a considerable period of time, lobular pneumonia develops, which may result in multiple abscesses.

DR. PONCHER.—The question is, Does the lung itself become infected? Or is it possible there is some local condition which causes weakness, and portions of that lung become atelectatic and thus more susceptible to secondary pneumonia?

DR. SANTE.—Do you recall the illustration of an autopsy specimen?

[The picture was thrown on the screen again.]

You will notice, as atelectasis occurred, it involved first one entire lobe, and then another lobe, possibly on the other side, and then the middle lobe, and so on. In other words, it was not a spotty involvement throughout the lung, but involvement of entire lobes. We followed a number of cases of ordinary massive atelectasis without manipulation of the patient, in which reinflation occurred, not as a massive thing, but as a spotty reinflation throughout the lung; an area of aeration occurring here and another there. Under these circumstances, the picture is one of bronchial pneumonia, and, if you had only one film and did not know what had gone before, you would say that it was bronchopneumonia.

Atelectasis plays a tremendous part in the course of pulmonary tuberculosis. It develops where small bronchi are occluded by granulations, giving rise to an appearance of consolidation; we think it is tuberculous infiltration, whereas it may be due in greater part to atelectasis. In this way there may be a tremendous involvement, and we may think it is due to scar tissue or to extensive tuberculous involvement; the area of atelectasis reinflates after absorption of the occluding infiltration, and we say that it was a wonderful example of resolution of massive tuberculosis process. I think it plays a greater part than we suspect in many ways with which we are not fully familiar.

DR. PONCHER.—I asked the question principally because I wondered if it were possible to prevent some of the secondary pneumonia by keeping the patient breathing well by change of position.

DR. SANTE.—I think that is the solution.

The administration of carbon dioxide after anesthesia has been very efficacious in our hands. If, in addition, you turn the patient over every two or three hours, so as not to let him lie in one position on his back, and do not overdose him with morphine or put a binder on his chest, there will be very little likelihood of development of massive atelectasis as a postoperative complication.

DR. PONCHER.—Do belladonna and codeine predispose to stasis? What is the early change in bronchial pneumonia?

DR. SANTE.—In bronchopneumonia there are clusters of infiltration about the bronchi, conforming to the pathologic picture one would expect to find.

I can see how administration of belladonna and morphine would favor the production of atelectasis. However, I do not recall any such case. I recall a case of atelectasis following a tonsillectomy in which the patient aspirated large quantities of blood while under the anesthetic. In such instances, atelectasis does not usually happen. The anesthesia is usually brief and of a type that puts the patient to sleep; he wakens, and his cough reflex returns immediately.

There is nothing unusual about the occlusion of the bronchus and the development of atelectasis; that was known long before x-rays were discovered. Lichtheim in 1870 put beans in the bronchi of rabbits and through transparent windows in the thorax watched what happened to the lung. With circulation intact he observed that there was progressive collapse of the lung. When the circulation was ligated and prevented from going to the obstructed portion of the lung, the air was not absorbed and atelectasis did not develop, thereby proving that it is the absorption of entrapped air by the circulating blood which produces the condition.

Roentgenologic Consideration of Acute Inflammatory Conditions of the Chest

L. R. Sante, M.D., St. Louis, Mo.

Perhaps the most important diseases of the chest which fall in this category are the pneumonias. In such conditions a thorough knowledge of the topography of the chest is essential to an understanding of the roentgenologic findings.

The left lung is divided into an upper and lower lobe, by an interlobar septum which slopes forward and downward from about the level of the fifth thoracic vertebra to the anterior chest wall near its diaphragmatic attachment. On the right side, the plane of a second interlobar septum extends horizontally forward from the hilum region to reach the anterior chest wall. If we indicate by diagram the relationship of the x-ray beam as it is projected during radiographic examination to these interlobar septums, we will find that the natural divergence of the x-ray beam centered about the region of the fifth or sixth thoracic vertebra will fall directly across the horizontal plane of interlobar pleura which separates the upper from the middle lobe. In consolidation of the upper lobe, therefore, we should have a uniformly dense shadow, homogeneous in character, with an abrupt straight line lower border extending across from the hilum to the periphery. Middle lobe consolidation should present a smaller shadow, extending from hilum to periphery with a straight line upper border and a lower margin which feathers out into normal lung density because of the wedge-shaped character of the lower margin of the consolidation. Lower lobe consolidation forms a large shadow which involves the lower two-thirds of the lung field, having a hazy upper as well as a hazy lower border. The left upper lobe corresponds roughly to the combined right upper and middle lobes so that consolidation of the left upper lobe could reasonably be supposed to result in a combination of the roentgenologic effects of consolidation of the upper and middle lobes, producing a shadow larger in size than the right upper lobe consolidation, and having a "feathered out" lower border.

Many types of atypical pneumonias occur, with partial consolidation of the various lobes and variations in course of the disease and in normal resolution. The Friedländer bacillus has a tendency to cause a peculiar sequence in lung involvement: it first causes bronchopneumonic involvement; these areas rapidly coalesce into pseudolobar distribution; this stage is often rapidly followed by extensive lung destruction and cavity formation; and healing, if it does occur, results in fibrosis.

The pneumonias are complicated principally by pleural effusion and actual lung destruction. The occurrence of a small amount of protective effusion is commonly found in pneumonia; this usually is absorbed within a short time without pus formation; if absorption is protracted, a tuberculous complication must be considered. If generalized empyema develops, the picture produced is typical; the mediastinum of children being freely movable, displacement of the heart and mediastinal structures to the opposite side is quite the rule. Pocketing of such effusions may occur, resulting in undrained regions of infection and continuation of fever. For detection of such foci roentgenology is most useful. No matter where they are found, there is one characteristic by which they can be recognized; they always bulge with a curved inner border in toward the compressible lung. Effusions of this sort may occur between the lobes as well.

Lung abscess with lung destruction occurs most frequently in children as a complication following tonsillectomy or as a secondary involvement following bronchopneumonia. Roentgenologically such infections appear as areas of destruction in the lung with surrounding areas of infiltration. It is remarkable with what rapidity the reaction clears up and the lung returns to normal after complete drainage, be that either natural by rupture into a bronchus and expectoration, or by surgical intervention.

At times multiple foci of infection in the lung may stimulate such a great amount of fibrous tissue that drainage may never be accomplished and chronic interstitial fibrosis may occur resulting in carnification of the lung.

MONDAY MORNING DISCUSSION

DR. JAMES W. BRUCE (LOUISVILLE, KY.).—Did I understand you to say you could not get the lipiodol into a lung abscess?

DR. SANTE.—I have never been able to introduce lipiodol into a lung abscess. I have seen one or two roentgenograms showing that others have succeeded in getting a small amount into abscesses, but only after drowning the lung, and it is rather rare.

The constriction of the outlet of the abscess by granulations and the fact that the abscess cavity is always filled with air or fluid make it almost impossible to fill with lipiodol.

DR. CHESTER A. STEWART (MINNEAPOLIS, MINN.).—You mentioned one case in which nontuberculous lobar pneumonia of the lung was followed by pleural exudate, which persisted and was apparently tuberculous in nature. Have you seen in nontuberculous inflammation a flare-up of an old tuberculous process?

DR. SANTE.—Yes; I have.

DR. STEWART.—With what conditions do you associate that?

DR. SANTE.—Any inflammatory condition may do it. The case I mentioned was not in a child, but an older individual, but it serves the purpose just as well. In another instance, a nurse in our hospital, about twenty-two years old, had what we thought of as hilus pneumonia, typical of pneumonic consolidation, with the crises and at least partial resolution. Her temperature went down to normal and stayed down for two weeks, and she was allowed to go back on the job. After she had been back at work about ten days, she began to have fever again, reaching as high as 102° F. We took another film and right in the center of the hilus shadow a round ring of destruction was found. We have never seen any such developments with pneumonia before. I could hardly believe that this was a cavity; I thought that perhaps it was a bronchus caught on end, a normal bronchus accentuated by the surrounding consolidation.

Roentgenograms were taken every few days, and in six weeks that cavity progressed from 1 cm. in diameter to, I should say, 6 cm. in diameter, and not until that time did we find tubercle bacilli in the sputum. She died of tuberculosis within a year's time. In my opinion this represents a case of activation of an old childhood tuberculous lesion.

Kornblum has demonstrated by roentgenograms taken over periods of months and years in individuals who have sustained caseous hilus glands from first infection with childhood tuberculosis which, years later, had invaded the mediastinum and caused tuberculous mediastinitis. Perhaps these tubercle bacilli lie dormant longer than we think.

DR. STEWART.—It has been our experience that they lie dormant for a long time and suddenly begin to advance after three or four years. They are nonprogressive up to a certain point, and then they begin to progress.

Have you correlated it with any nontuberculous infection like the case you mention now?

DR. SANTE.—Do you mean a person having a nontuberculous lesion, supposed to be quiescent, and suddenly, after respiratory infection, it starts again?

DR. STEWART.—Yes.

DR. SANTE.—I think it would be hard to say. So often those things happen without apparent reason, without the respiratory infection. Some physicians say that, if tuberculous individuals have respiratory infection and get by with it, they are better off, as far as their tuberculous infection is concerned. I cannot quite agree with this, however, but I feel that the clinician would be in a much better position to judge than I.

DR. STEWART.—Did they make any biologic studies on the original hilus thing you saw that you thought was pneumonic? I meant, was it pneumococcus?

DR. SANTE.—Yes, in this instance pneumococci were found. There is another type of recurrent hilus consolidation which occurs in children with which you are all familiar, I am sure. It is not mentioned much any more; I have not seen it in the literature for years. Fifteen or twenty years ago there was a series of articles in Italian literature, if I remember correctly, on recurrent hilus tuberculous pneumonia in children.

It was characterized clinically by an exacerbation of fever and accentuation in appearance and size of the hilus shadow with subsequent subsidence of symptoms; then three or four months later, from no apparent cause or perhaps after a slight cold, there would be a flare-up of the condition. Actual lung punctures into the hilus regions have been done in such cases with recovery of tubercle bacilli. This sequence of events was ascribed to the repeated breaking down of small tuberculous foci that were undoubtedly of childhood origin in the hilum lymph nodes.

I wonder if any of you have seen acute glandular tuberculosis in an adult? I have seen it in children, but never so pronounced as it was in this case which I am about to describe. Most of us think of glandular tuberculosis as being due to a more or less different strain of organism, possibly, than the pulmonary type. I had a young man who had worked in my department for ten or twelve years. He had a wife and two children and was perfectly healthy; he had never been off a day on account of illness during this entire time. One day he came to me and said, "Feel this little kernel under my chin." It was the size of a pea. I inspected his mouth and face to see if any source of infection could be found, but nothing was present which could have accounted for the gland. I told him to put some hot applications on it and return the next day; that was on a Friday afternoon. I did not see him on Saturday, and when I saw him at the hospital on the following Monday, three days later, he had masses of glands as large as your fist in the cervical regions.

I thought of acute Hodgkin's disease. A gland was removed and sent for examination to three pathologists in St. Louis. Without hesitation the diagnosis on each instance was tuberculosis of the glands. I could not understand it, developing as it did within three days from the original onset.

A tuberculosis expert recommended x-ray therapy and I gave him a tenth of a dose ordinarily given in such cases. In an hour's time he had a chill followed by a temperature of 104° F. The wound which remained after biopsy showed tubercle bacilli and did not heal for three or four months.

After he had been free from temperature for some months, further x-ray treatment was given, gradually increasing the dosage up to the usual amount. Ultimately the enlargement of the glands subsided; all symptoms disappeared; the wound healed; and he came back on the job.

He had been back for two months when one day he complained of pain in his back. X-ray examination of his spine revealed at the margin of one of the vertebrae an area of apparent destruction. A plaster cast was applied, but he insisted on continuing to work.

Since at that time, because of economic conditions, he could no longer support his wife and two children on the salary he was getting, he left the institution and went to work as an automobile salesman. About a year later he came to me, and x-ray examination showed that he had complete destruction of several vertebrae and the adjoining cartilage from tuberculosis. He has been in the hospital on his back for two years.

This is one of the most acute cases of glandular tuberculosis I have ever seen. Of course, it has nothing to do with pulmonary diseases, but it relates to the thing we are discussing.

DR. STEWART.—Had he a tuberculin test previous to that?

DR. SANTE.—I do not know; I do not think he was ever tested—he was always perfectly healthy. His chest film was normal and has remained so.

DR. STEWART.—What happened ultimately? Did he die?

DR. SANTE.—He is still alive, but a cripple.

DR. MAURICE J. SEARLE (TULSA, OKLA.)—I was interested in the remark Dr. Sante made as to the apparent ease with which lipiodol could be introduced by the postnasal route. I think emphasis should be laid on the potential danger, in lung pathology, of the continued use of oily sprays, mineral oils and such, in the nose.

DR. SANTE.—There have been a number of cases of lipoid pneumonia reported, in which the lung was completely filled with lipoid material resulting from nose sprays and the administration of cod liver oil. There have been cases of this type which were fatal. The most common instance of involvement of lung is the postnasal drip in chronic sinus infection, producing lung pathology. This is a graphic illustration of the fact that secretions from the sinuses may actually be aspirated into the lung.

DR. JOHN R. VONACHEN (PEORIA, ILL.).—Have you had any experience with infants between the ages of nine months and a year and a half with the history that at the outset there is a hollow cough which does not respond to any usual medication? The x-ray picture shows a convex shadow at the thymus area, not, however, a general widening on both sides. This shadow is to the right. There is no history corresponding to congenital heart disease. In the three cases we have had, we thought of the possibility of abnormality of the great vessels. Peculiarly, in two of the cases, there has been no history of previous infection, but the hollow cough persists over a period of months. The infants have responded to x-ray treatments. There was no history of previous thymic symptoms.

DR. SANTE.—I dare say you refer to an increased density of the superior mediastinum from the thymus.

[Dr. Sante referred to four of the slides previously shown exemplifying the condition referred to by Dr. Vonachen.]

The thymus is so varied in its appearance that you have to be very careful before you say that the thymus you see is the thing that is causing the cough and the trouble. The observations of many radiologists in making examination in the regular course of respiration have shown that the thymus in children changes in size very readily. In one of those pictures during one period of respiration, there is no enlargement of the shadow; it is perfectly clear, and you would not think there was any enlargement at all. One patient might show a large shadow and yet would have no symptoms whatever, while another in whom there were symptoms of thymic pressure would have no x-ray indication.

In my opinion, x-ray films, so far as thymus symptoms are concerned, must be judged merely as a confirmatory measure. I do not go so far as to say that enlargement of the thymus in an infant never causes trouble, but I certainly would not advocate that every newborn infant receive treatment for his thymus gland, as has been recommended in some hospitals. I have never seen any ill effects produced in the infant by the small doses that we give for thymic enlargement. There has recently been some question raised as to the ultimate effect on successive generations. I think that such effect is largely theoretical, but it certainly is something which must receive our closest consideration.

DR. BLESSING.—Dr. Brennemann has taught that the correct way to localize lobar pneumonia is to go over the chest carefully, weigh all the factors, decide on the location of the pathology, draw a diagonal line through the chest, *and take the other end.*

DR. SANTE.—This is not a matter of criticism. The difficulty of diagnosis of lobar pneumonia in children is well known. I showed slides which illustrated several cases in which the roentgenogram has not told the whole story. I feel that a clinician, knowing that and being fully aware of it, will go over the chest repeatedly and compare his physical findings with what he sees in the roentgenogram and in that way will become a much keener clinician in the diagnosis of chest conditions in the future.

DR. CLINE.—I am sure we feel indebted to Dr. Sante for his excellent discussion on this subject. He has told us of several instances in which he depends upon the internist to help him, and undoubtedly there are many times when we expect the x-ray man to help us.

Dr. Blessing mentioned the difficulty of diagnosing pneumonia. The asthmatic child is just as much a problem. His respiratory rate is increased. Careful physical examination of the chest suggests an oncoming pneumonia. You as the physician relate your findings and provisional diagnosis to the parents. The next day, however, as you enter the household for your professional visit you are astounded to have the little patient greet you at the front door. Physical examination of chest at this time presents a fairly normal picture.

Recently I had four asthmatic children in two days. In one case I wondered if my diagnosis were correct. I was sorry I did not get an x-ray picture. This child was seven weeks old. He had no fever, his throat was red, and respirations were rapid and labored. A foreign body naturally was one of my first thoughts since there were older children in the house who through their play might have been responsible for the introduction of the foreign body. However, there were no unilateral findings on physical examination of this baby's chest. The mother, however, gave a definite allergic history in that she herself was an allergic eczematous baby and that with this new baby she had had feeding difficulties. The physical findings of the lungs were quite like those of what we would expect to find in an older child with asthma. I felt safe in administering a small dose of adrenalin, which I did, and within about ten minutes the baby showed a great improvement just as we have seen numerous times after the administration of adrenalin to the typical asthmatic patient. His respiratory rate became greatly decreased, the prolonged expiratory phase with the numerous musical râles almost immediately improved, and the baby soon went to sleep. The next morning he was fine. This is not the first example of immediate relief with a dose of 0.15 c.c. of adrenalin given to these small babies.

Again I want to express our appreciation to Dr. Sante for his wonderful presentation this morning.

TUESDAY AFTERNOON DISCUSSION

DR. ANDERSON.—Are you able to diagnose bronchiectasis without lipiodol injection?

DR. SANTE.—In some instances it is suggestive, but, as a rule, one would rather see the definite, characteristic picture produced by lipiodol injection before an absolute diagnosis is made. Without lipiodol injection one would have no way of distinguishing the condition in many instances.

DR. ALFRED BIGGS (CHICAGO, ILL.).—Does the injection of lipiodol injure the lung tissue?

DR. SANTE.—There is evidence that lipiodol remaining for a long time in contact with closed, serous cavities can cause damage. You may not be familiar with the study that was made of the injection of lipiodol in the pericardial sacs of dogs. It was allowed to remain in the pericardial cavity for considerable time, and when the dogs were killed and the pericardium examined, it was found in every instance there was an exudative pericarditis from the long contact with lipiodol.

There are other experiments on record in which lipiodol was used to try to define the inside of the knee joint, wherein a number of human beings were injected. There was no drainage from the knee joint, and the oil remained for a long time in contact with the serous membrane. A paper was published warning against its use for this purpose on account of the adhesions which resulted.

Then, too, there is the experience of a number of neurologists who injected large amounts of lipiodol into the spinal canal to detect the presence of spinal cord tumors; it was found they had encysted masses of oil after a number of months.

On the basis of these experiences, we thought it might be a good idea to see if the way we were drowning lungs with lipiodol might be causing injury to the lung tissue. We injected some dogs. These were killed at various intervals months later, after a considerable period had elapsed. Pathologic examination of sections taken from these areas failed to disclose any evidence of real injury in the lung. Here there is a definite mechanism for removal of foreign objects. The whole bronchial tree is subject to the irritation of foreign bodies. There is the mechanism of the cough reflex to take care of part of it, and there is the further mechanism of actual phagocytes to pick up the particles from the alveoli and carry them into the lymphatics and get rid of them. That is one reason the lung is less likely to be affected by this medication.

DR. WHITAKER,—Do you find many instances of empyema associated with lung abscesses in children?

DR. SANTE.—That does occur, but it is not very common.

DR. WHITAKER.—It has been reported that it occurred practically always in the periphery of the lung.

DR. SANTE.—Perhaps the term "lung abscess" in that instance may be used rather loosely to mean a localized collection of pus. You have heard surgeons say, "I am going to operate on a lung abscess," when he referred really to a localized collection of pus between pleural layers. We can define an abscess as actual breaking down or destruction of the parenchyma of the lung, whereas many surgeons speak of lung abscesses as localized collection of pus in the pleural cavity, such as I showed, with the rounded borders.

Localized pocketing is very commonly associated with a generalized pleural effusion. The fluid in the general cavity is operated on, drained, and the patient's

temperature comes down, only to be followed by a subsequent rise. These are the classical symptoms of pocketing of effusion; the collection has to be ruptured, or it may rupture itself, or it may be attacked with surgical procedure.

There is another condition which more frequently prevails. You have all seen actual abscess of the lung in which the lung parenchyma was destroyed; there was a development of an associated pleural effusion in the general pleural cavity, and tapping the pleural effusion elicited, not pus, but clear fluid. Microscopic examination of the fluid showed many leucocytes, indicating that it was simply sympathetic effusion as the result of the deep-seated infection. The same may be true of an abscess under the diaphragm.

DR. WHITAKER.—If the diagnosis is correct, it is all right to puncture an empyema. If there is an abscess, it may be wrong to puncture the pleural cavity, but, since there is already infection, no real harm is done.

DR. SANTE.—I have seen a number of instances in which lung abscesses occurred from emboli after tonsillectomy at the margin of the interlobar pleura. The autopsy showed that what was thought to be a lung abscess was effusion in the interlobar space. I think such x-ray findings are subject to much variation, and the observation of one is just as good as another.

DR. ANDERSON.—With reference to those pictures which you showed of pneumonia following a shoulder injury—often a child who has been running a temperature and is sick is brought to us; the parents say he has had a fall, and they think that is the reason for the temperature. I wonder if the reason the child falls is that he is coming down with an illness, and is dizzy and cannot maintain his balance.

DR. SANTE.—In the instance illustrated, we had taken a roentgenogram of the injured shoulder to see if there was a fracture, and the examination showed nothing whatever the matter with the lung. Three days elapsed before pneumonia developed. I am almost sorry I introduced the films of pneumonia following trauma. Please do not say I spoke of trauma as being in the slightest degree the cause of lobar pneumonia, because considerable searching of a great number of cases resulted in my finding only three such cases. When the condition is found in such small proportion, I think one is almost justified in calling it coincidence.

DR. HUGH C. GRAHAM (TULSA, OKLA.).—What is your technic in giving lipiodol to older children?

DR. SANTE.—In looking for bronchiectasis, we use the old supraglottic technic, dropping it on the back of the tongue with a syringe. By pulling the tongue well forward and using a curved cannula, you can observe injection better. For bronchiectasis we usually put it in one lung and then in the other, injecting the more suspicious lung first.

We put two bricks under the legs of one side of a chair to tilt it so that the patient has to sit sideways, tilted toward the side opposite the lung that is to be filled, putting the bricks under the right side, if it is the left lung that is to be filled, and vice versa.

You noticed catheters in the lungs in some of the roentgenograms. A large ureteral catheter is used only in special cases where we want to observe the lipiodol at the time of injection under fluoroscopic control. It is hard to use a catheter with a child. We have tried also to use an intubation apparatus, and it is difficult. In older patients it is possible to insert a catheter into the lung. The only trick to it is to put the catheter in ice water because you have to make a hook on the end of the catheter so it will go down the trachea. If you do not have it cold, it will straighten

out and go down the esophagus. A little cocaine is injected through the catheter if the patient starts to cough—and, of course, he will—as it enters the glottis. The catheter is not straight, and once introduced the point of the catheter can be directed wherever you please by rolling it between the fingers. If it does not go in right, you can place it under fluoroscopic control, inject slowly and watch everything. Sometimes with a catheter the patient will cough a good deal, but ordinarily an adult will not cough very much. It is almost impossible to use this method in young children.

Usually there is very little trouble with an adult for ordinary supraglottic injection unless the patient has a nervous or irritative cough. In such cases you have to cocainize because the patient is so apprehensive that he will not do anything you tell him. We have handled many cases without cocainizing at all.

Chairman Barnett expressed the thanks and appreciation of the group to Dr. Sante for his presence at the meeting and for his instructive and interesting discourse.

The meeting was adjourned at four-thirty o'clock.

SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MAY 11 AND 12, 1936

Panel Discussion on Resistance to Tuberculosis During Childhood

C. A. Stewart, University of Minnesota; Chairman.
L. Dienes, Massachusetts General Hospital, Boston; Immunology.
H. A. McCordock, Washington University, St. Louis; Pathology.
J. A. Myers, University of Minnesota; Clinical Medicine.
H. C. Stewart, Department of Public Health, Tennessee; Epidemiology.

Normal Resistance or the Reaction to First Infection

CHAIRMAN STEWART.—Dr. Myers, what do studies in your special field indicate as to the ability or inability of children to control and to survive first infection with virulent tubercle bacilli?

DR. MYERS.—Mr. Chairman, actual recent observations have shown that children have splendid ability to control and survive the first infection with virulent tubercle bacilli. Our earlier impressions with regard to the high mortality of tuberculosis among children, particularly infants, were based largely upon observations of children sufficiently ill to require the services of physicians or to be hospitalized. We now know that the majority of such children were not suffering from the first infection type of tuberculosis but from reinfection forms of disease which developed on sensitized tissues, such as meningitis, miliary disease, and tuberculous pneumonia. With the more modern methods of detecting the presence of tuberculosis in children, such as the tuberculin test and the x-ray film, we have learned that most children who develop the primary complex in infancy or in childhood demonstrate a powerful resistance against it. A positive tuberculin reaction is sufficient evidence to justify the diagnosis of first infection type of tuberculosis in the human body. The lesions may be so located or of such size that the physical examination, including the x-ray film, does not aid in the detection of their location; nevertheless they exist. The fact that most children who react positively to the tuberculin test have had no significant illness due to tuberculosis and approach the period of adolescence with no external manifestations indicates that the child has ample ability to control and survive first infection type of tuberculosis per se. After tubercle bacilli find lodgment in the body of a child, a period of three to seven weeks elapses before the tissues have become sufficiently allergic to tuberculo-protein to react positively to the tuberculin test. The fact is well established that earlier than this allergy is developing but does not reach such a degree as to be detected by the test. During this period of time, the framework of tubercle formation is well laid down, but up to this time there is no symptom of the disease. In the occasional case, however, one may recover tubercle bacilli from the gastric contents before allergy appears, as did Ligner. About the time allergy has reached such a degree as to produce a positive tuberculin reaction, there may be a temperature elevation which persists for a few days to a few weeks. Along with this is a definite increase in the red cell sedimentation rate. In some cases even erythema nodosum appears. After the fever subsides, the sedimentation rate continues to be increased but in a few weeks returns to

normal. The fever due to first infection type of tuberculosis may not be noticed by the child or parents, or it may be attributed to acute respiratory infections, etc. Again, there may be no temperature elevation. Most children who have the first infection type of tuberculosis and subsequently have it detected by the tuberculin test, as well as their parents, have no idea as to when it developed, the symptoms having been slight or entirely absent. Nevertheless, tuberculosis of the first infection type is a definite disease entity.

In a small percentage of children who develop the first infection type of tuberculosis, one is able to find on x-ray film examination a pneumonic area in the lung about the time the tuberculin test becomes positive. This area may be so small that it is barely detectable by an x-ray film examination; again, it must be large so as to involve the greater part of the lung. Even when such massive involvement is present, often the symptoms are insignificant or entirely absent. In our experience whether or not treatment is instituted in such cases, the lesions come under control while the children appear perfectly well. The shadows slowly disappear, and usually the only evidence of their previous existence is that of deposits of calcium or Ghon tubercle formation in or near the center of the previously existing pneumonic area, in addition to similar deposits in the regional lymph nodes. We have not seen a single death attributable to uncomplicated first infection type of tuberculosis.

In all probability, the natural defense mechanism can be overwhelmed, as may have occurred in the Lübeck disaster, but even among those infants death probably occurred from reinfection form of tuberculosis after allergy was established rather than from the first infection type. It is doubtful whether natural resistance is ever overwhelmed by the number of tubercle bacilli which the child ordinarily first takes into his body through exposure to tuberculous patients. However, at some subsequent time, the bacilli in the lesions of the primary complex may proliferate and break prison, or new bacilli may be taken into the body from exogenous sources; whereupon they are present in such large numbers, which, together with the handicap of the presence of allergy, results in overwhelming the defense mechanism and destructive reinfection forms of the disease appear.

CHAIRMAN STEWART.—Dr. H. C. Stewart, what studies in your special field indicate the ability or inability of children to control and to survive first infection with virulent tubercle bacilli?

DR. H. C. STEWART.—First, it should be understood that our fields of work have been somewhat different. Dr. Myers and his associates have been engaged in the study of tuberculosis, particularly as infection and disease affect children, over a longer period of time than is the case in the Tennessee studies.

The area under study in Tennessee is a thoroughly rural community, and information is being collected which is directed toward tuberculosis in all ages. Data from this area with particular reference to first infection, as yet, have not been compiled in detail. In Tennessee, as in other areas, the period of childhood is the age period of life in which there is the greatest increase in the numbers of individuals acquiring a first infection. It is also to be noted that this age period is the one in which the recorded death rate for tuberculosis is the lowest. A rather high incidence of tuberculosis deaths in proportion to population of the same age group is noted in early life. In the next older groups of children, covering about a decade, the death rates from tuberculosis are very low. It seems evident that in a population mass, although children are receiving sufficient dosages of tubercle bacilli to render them allergic, they are not suffering from a severe type of tuberculosis, at least not so severe as to be demonstrated by the reporting of a large number of deaths from tuberculosis in the same age groups.

Numerous children have been observed during the progress of the tuberculosis study in Williamson County. The household is used as the unit of study. Naturally,

the frequency of reexaminations of these children has been a matter of importance, and of increasing importance with the continued adding of households for study. Limitations of finances, personnel, and time impose certain restrictions in follow-up and reexamination activities. When these activities can be so spaced as to allow a longer period of time to elapse, a larger number of individuals can be kept under observation. However, it is of importance that observations be made at sufficiently frequent intervals that important changes in physical status will not be overlooked. In the study area to which reference is made, it seems that these children have very little or no inconvenience as the result of a first infection with the tubercle bacillus. Many of these children have been examined repeatedly, and no changes have been noted. Many children examined show evidence of infection on the x-ray film as evidenced by calcified nodules in the lung parenchyma or tracheobronchial calcification; yet it is impossible to ascertain when this infection was acquired, and, furthermore, it is impossible to state a probable time of life when this acquired infection was going through the stages which later resulted in the observed calcification. As a result of these observations, reexaminations of children up to adolescent ages have been lessened in frequency with the feeling that no significant changes were likely to occur.

With the points mentioned taken into account, it would seem that children between the ages of infancy and adolescence are able to control and survive first infections with tubercle bacilli.

CHAIRMAN STEWART.—Do you rate normal resistance, then, as good, fair, bad, indifferent? Or how do you rate it?

DR. H. C. STEWART.—Normal resistance in these age periods is good.

CHAIRMAN STEWART.—Dr. McCordock, will you tell us what pathologic changes occur in the body following infection, and trace these changes from the initial deposit of bacilli to tubercle formation?

DR. McCORDOCK.—Primary tuberculosis of childhood has been intensively studied for the past half century. Even before the discovery of the tubercle bacillus, Parrot described the focal pulmonary nodule and the associated nodules in the tracheobronchial lymph nodes. Ghon and Roman later showed that this combination of a fibrocaseous or calcified nodule in the lung and similar involvement of the hilum nodes was the result of primary infection. It was subsequently termed the primary complex by Ranke.

The prevailing opinion at present is that in the majority of instances infection takes place through the inhalation of tubercle bacilli. No adequate study can be made of the initial reactions to the first infection in the human lung, because early microscopic lesions cannot be obtained. However, it seems likely that the early reactions in children are similar to those observed in experimental first infection in animals. Two opinions are held concerning the initial type of reaction to a primary infection. One group of investigators claims that a proliferative fibrous tubercle is always first produced, and another maintains that the primary response is a focus of inflammatory pneumonia. From both experimental work and the study of older human primary lesions, it seems probable that the initial response may be of either type, depending upon several factors, but principally upon the numbers of bacilli involved. Large numbers produce a focus of pneumonia while fewer organisms call forth tubercle formation.

The number of bacilli in the primary focus, whether they represent a massive initial infection or develop from the growth of a small original dose, determines to a large degree the final outcome of childhood tuberculosis. Other factors being equal, a healed primary complex with minimal dissemination to distant organs and an

active immunity are the usual results of primary infection with a small number of bacilli. An overwhelming dose produces progressive tuberculosis which ends fatally. Between these two extremes must be placed those cases in which the bacilli are almost too numerous to be held in check by the degree of resistance developed. These are the children who run a protracted course, finally succumbing to some acute form of tuberculosis, or in the end arresting the progress of the disease, after extensive destruction and scarring of tissue.

The first cellular reaction to the presence of tubercle bacilli is a transitory accumulation of polymorphonuclear leucocytes. Within a few hours large mononuclear phagocytes begin to appear and continue to increase in numbers until at the end of twenty-four hours this cell predominates in the exudate. When only a small number of bacilli lodge in the lung, they are all promptly engulfed by mononuclear cells, which later migrate into the interstitial tissue and finally enter the nearest lymphatic. Some of these mononuclear phagocytes, with their burden of bacilli, reach the tracheobronchial lymph nodes; others become arrested in the tissue spaces of the alveolar or bronchial walls. Indeed, a few of these cells carrying bacilli may pass through the regional nodes to enter the thoracic duct, and eventually reach the circulation through the subclavian vein from where they may be transported to any organ in the body. Tubercles develop about these bacilli-laden cells wherever they lodge.

When large numbers of bacilli are present, many of them remain in the alveoli and call forth masses of mononuclear cells. A study of postmortem material seems to indicate that this focal mononuclear cell pneumonia is the usual type of reaction in children to first infection. Necrosis followed by caseation appears in the exudate after sensitization or allergy develops. It has been estimated that children become allergic in from three to seven weeks after the primary infection.

In addition to sensitization, acquired resistance or immunity also develops after the first infection. This inhibits active growth and multiplication of tubercle bacilli. The mechanism of this restraint is not clearly understood, but it is probably due to some incompatibility that develops between the tissues of the host and the bacilli, similar to that observed in the natural resistance which cattle and rabbits possess to the human type of bacillus. The length of time necessary for the development of acquired resistance in man is not definitely known, but in animals it can be demonstrated soon after the appearance of allergy.

In the early stages of the first infection, before the appearance of acquired resistance, the bacilli can grow without much restraint. There is thus an interval between infection and the development of acquired resistance during which the bacilli are able to grow unhampered by the defense mechanisms later mobilized by acquired immunity. This period of unrestrained growth is enjoyed not only by the bacilli remaining in the lungs, but also by those that have been carried to distant organs. A delay in the development of acquired immunity prolongs this initial period of active bacillary growth and may explain the presence of large caseous foci in some children who, to start with, have received only a relatively small infecting dose of bacilli.

Primary infection in children is generally looked upon as a process which is localized to the lungs and regional lymph nodes. A study of autopsy material, however, reveals the fact that in most instances this is not the case. Isolated tubercles can usually be found in other organs. They are most readily observed in the spleen and liver, but, if sought, they often can be found in such organs as lymph nodes, bone marrow, kidneys, adrenals, and brain. It is important to understand that this dissemination takes place during the first infection, for it paves the way for the later development of tuberculosis in organs distant from the lungs. Tuberculous meningitis and osteomyelitis, as well as many other nonpulmonary secondary mani-

festations, are usually the late result of a primary dissemination and may occur at a time when the initial lung foci are quiescent or even completely healed.

CHAIRMAN STEWART.—I shall ask Dr. Dienes how he explains the reaction to the first infection from the immunologic point of view.

DR. DIENES.—Dr. Myers pointed out that children, as a rule, resist the first infection with tubercle bacilli very well and added that this is probably due to the natural defensive forces of the organism. I think this should be interpreted to mean that the same mechanism comes into play in tuberculosis as in other infectious diseases which usually heal without causing permanent injury. The organism responds to the infection by developing specific immunity, and healing probably depends on this response.

The course of the disease indicates that a high degree of immunity develops soon after infection. When the first lesions break down, virulent tubercle bacilli are eliminated. These pass through the bronchi and the alimentary tract without producing new lesions as would be the case in a previously noninfected organism. The early appearance of tuberculin sensitiveness also indicates that the specific immunity response develops soon after infection.

Animal experiments show very well the importance of specific immunity. Lurie, a collaborator of Opie, recently made a careful study of the reaction of rabbits to intravenously injected virulent and nonvirulent tubercle bacilli. The bacteria are deposited in the different organs in various amounts and at first multiply in all organs. But after the immunity response starts, the multiplication of nonvirulent human bacilli is checked in all organs and slowly they are destroyed. A few small lesions remain, however, in which the bacteria continue to multiply. The bovine bacilli are virulent for rabbits. Their multiplication is, nevertheless, checked, and they are destroyed in certain organs such as the bone marrow, liver, and spleen, but they continue to multiply unchecked in the lungs and in the kidneys.

These observations illustrate two important characteristics of the immunity to tuberculosis. In the first place, they show that, when the immunity response starts, the organism is able to check the multiplication of the bacilli and the lesions heal. In the second place, it shows that the effectiveness of the immunity response depends to a large extent upon the local tissues. The bacteria are destroyed in certain organs but not in others, regardless of how heavy the original infection was. I have observed similar conditions in guinea pigs, but in these animals the most sensitive organs are not the kidney and lung, but the liver and especially the spleen. If the lesions grow beyond a certain size before the development of immunity, the healing even after infection with avirulent bacteria is very slow, and the lesions in the lung sometimes extend by the heavy infection of the surrounding tissue. Animal experiments give strong support to the view expressed by Dr. McCordock that the dissemination of tubercle bacilli before the development of immunity is responsible for the development of secondary lesions.

The immunity response in tuberculosis has been considered for many reasons quite different from the immunity response in acute infectious diseases. Upon closer examination it becomes apparent that the differences are only of degree. For instance, in tuberculosis the organism is not able to get rid of the infection; a small lesion remains probably through life, and it may flare up in a later period of life. The immunity lasts only as long as lesions are present which contain virulent bacteria. Such conditions are not only found in tuberculosis but they may be present in acute infectious diseases as well. In rabbits the vaccinia virus persists in the organism after healing of the lesions, and immunity lasts only as long as the virus is present. In this respect, one of the most typical acute infectious diseases, vaccinia, is similar to tuberculosis.

In tuberculosis besides antibodies strong tuberculin sensitiveness develops; this is regarded by many authors as an abnormal manifestation of the specific immunity response. From a long study of tuberculin sensitiveness I came to the conclusion that allergy represents the development of active immunity in the tissues all over the organism. Since this conclusion is based on the observation of new facts, it is not merely a variation of formerly expressed opinions. The most important new observations are the following: the development of purely active tissue hypersensitiveness before the appearance of antibodies after injection of simple antigens like egg white or horse serum; the correspondence of local tuberculin reactions both grossly and microscopically to the local reactions in the previously mentioned preanaphylactic hypersensitiveness; the observation that tuberculosis and certain other diseases increase the intensity of the immunity response. In tuberculous guinea pigs egg white produces, under appropriate conditions, large necrotic skin reactions comparable in every respect to tuberculin reactions.

On close examination it seems probable that in the healing of the first tuberculous lesions the specific immunity plays a part similar to that in the healing of other infectious diseases. In tuberculosis and in certain other diseases the active immunity of the tissues is probably more important than are the free antibodies.

CHAIRMAN STEWART.—How early do immunologic changes appear?

DR. DIENES.—It depends to a great extent on the size of the infection. If a guinea pig is infected with a large dose, allergy appears in less than three days.

CHAIRMAN STEWART.—You have talked about allergic change. How early does it appear in man?

DR. DIENES.—In man, one is forced of course to rely solely on clinical evidence. I do not believe, however, that the skin reaction ever becomes positive within the first two weeks after infection, and probably the period is usually longer.

CHAIRMAN STEWART.—Is the reaction in first infection mainly normal resistance, or is it mainly acquired resistance?

DR. DIENES.—I believe it depends to a large extent on what we call acquired resistance and what we call normal resistance.

CHAIRMAN STEWART.—What would you be inclined to say?

DR. DIENES.—To a large extent it is acquired resistance because the resistance to reinfection is largely increased at the time when the lesions begin to heal.

CHAIRMAN STEWART.—Does the immunity response accelerate a process that occurs normally?

DR. DIENES.—Yes, I believe that acquired resistance depends in most cases on an acceleration and an intensification of the process which would also occur to a certain extent without specific immunity. This intensification and acceleration of the defensive processes, however, make possible the resistance to the infection.

CHAIRMAN STEWART.—Dr. Myers, are preventoriums and summer camps necessary for the treatment of primary tuberculosis?

DR. MYERS.—Negro, Mexican, and American Indian children control the primary complex just as quickly and effectively as white children. Moreover, children from families in whose homes hygiene conditions are bad, control the primary complex in the same manner as those from the best homes. Paradoxical as it may seem, children treated in special schools and classrooms, preventoriums, and sanatoriums do not show any difference in the rapidity or effectiveness of the control of the primary complex than children who remain in the homes after contact is broken and engage in all of the activities with the normal children of the home and the community.

Summer camps, such as those operated by luncheon clubs and religious organizations, are worth while for all children, but as a tuberculosis control measure the summer camp is worthless and may even give to parents a false sense of security. Even if children with the first infection type of disease required treatment, the time spent in a summer camp is too short to be of any avail. I can see no justification whatsoever for the expenditure of funds to operate summer camps—funds raised through the sale of Christmas seals or appropriated by officials of political divisions or secured in any other manner to fight tuberculosis. The summer camp is a misdirected activity and is a remnant of the day when we knew little about the nature of the first infection type of tuberculosis and when our activities were based upon opinions rather than facts.

CHAIRMAN STEWART.—Dr. H. C. Stewart, do you feel that preventoriums and summer camps are necessary for the treatment of primary tuberculosis?

DR. H. C. STEWART.—My experience in that field has been extremely limited. From the figures and observations cited, it would seem that preventoriums and summer camps are not necessary for the treatment of children with first infections by the tubercle bacillus.

CHAIRMAN STEWART.—Dr. Myers, how do you rate normal resistance?

DR. MYERS.—Inasmuch as we see the same defense mechanism attacking the tubercle bacilli of first infection in all races of people and at all ages in the span of life, and find a similar mechanism at work in a number of animal species that have been carefully studied, I am firmly convinced that it is the natural defense mechanism rather than any specific immunity which brings tuberculosis of the first infection type under control in such a high percentage of the individuals attacked by tubercle bacilli. The defense mechanism consists, first, of the neutrophiles, which ingest and focalize tubercle bacilli. As the neutrophiles die, they are surrounded and ingested by the monocytes, which soon become epithelioid cells. Next, there appears around the developing tubercle a wall of lymphocytes, the local connective tissue cells proliferate, and a fibrous wall is laid down; lime salts may be carried into the tubercle and finally invade the fibrous tissue capsule; even true bone may be deposited in this capsule. This, in brief, is the defense mechanism against tubercle bacilli. It has also been shown to be the defense mechanism against inanimate objects of the particulate type, such as particles of silica. Therefore, it is not a specific reaction against the tubercle bacillus but the natural resistance which the body ever has present to defend itself against invasion from microorganisms and inanimate objects. How far the defense mechanism must carry its work depends upon the nature of the invader. If it is a pathogenic microorganism easily destroyed, there is no need for the laying down of the fibrous wall; on the other hand, if it is one which cannot be destroyed, such as the tubercle bacillus or particles of silica, the defense mechanism continues its work until adequate walls are laid down to protect the remainder of the body against invasion.

CHAIRMAN STEWART.—Dr. H. C. Stewart, after hearing what Dr. Myers has said, is there any point you would tend to modify, or would you be inclined to agree in general with that?

DR. STEWART.—I would be inclined to agree in general with what Dr. Myers has said with regard to the ability of children to withstand primary infections.

CHAIRMAN STEWART.—We are talking about normal resistance. Dr. McCordock, from what you have seen in the study of pathology, how would you rate the ability of the child to control first infection?

DR. McCORDOCK.—The majority of children, fortunately, are able to control the primary infection extremely well. This group includes those children who probably receive a moderate infecting dose of bacilli, and the primary lesions are quickly healed without widespread pulmonary dissemination or the transportation of bacilli to distant organs with the consequent production of secondary tubercles.

A small percentage of children do not control the first infection but die of progressive pulmonary lesions or of an acute tuberculous process in some other organ before the primary focus is arrested. These may represent children who in the beginning are infected with an overwhelming dose, which, for instance, may be acquired readily in childhood by intimate contact with an adult who has an active pulmonary lesion, or children whose immunologic defense mechanism fails to develop quickly enough to prevent a small initial dose from multiplying into a large one.

A third group of children succeed in arresting the primary lesions but secondary foci remain active. The secondary lesions are usually the result of a metastatic dissemination during the period of primary infection, but in the case of chronic pulmonary tuberculosis the possibility of exogenous reinfection cannot be denied. This is the group of children who develop subacute or chronic tuberculosis of some organ which, of course, may eventually heal. However, the sudden development of an acute tuberculous process, such as meningitis, peritonitis, or a massive tuberculous pneumonia, is always a hazard and often proves to be the terminal event in children of this group.

The essence of this question is not the ability of the host merely to control the primary infection by developing an encapsulated primary complex, but to be able to do so without the production of extensive secondary metastatic tubercles which remain latent foci that are often responsible for the sudden flare-up of a subsequent tuberculous process.

Acquired Resistance or the Reaction to Reinfection

CHAIRMAN STEWART.—I shall ask Dr. Myers what he considers to be the chronologic order of the events that lead to the development in man of reinfection (secondary) forms of tuberculosis of exogenous or endogenous origin.

DR. MYERS.—Before the reinfection forms of tuberculosis can develop, the first infection type of disease as previously described must be established; therefore it is important to differentiate, so far as possible, between first infection and reinfection forms of disease. When periodic tuberculin testing has been done among negative reactors so as to detect allergy soon after it appears, one is usually justified in considering lesions which appear in the lung within a few weeks after allergy is established as of the first infection type, whereas lesions which first make their appearance six months or more after allergy develops usually are of the reinfection type. In many cases, however, allergy already is present at the time of the first examination, and lesions which are seen at the same time in such a stage as to cast a homogeneous or even mottled shadow on the x-ray film may be due to either the first infection or reinfection type of disease. For the time being, we have no way of differentiating between them. The patient may be entirely free from symptoms with either type of disease; therefore it becomes a matter of making careful periodic examinations, including x-ray films, to determine subsequent changes in the lesion. If it proves to be of the first infection type, there will appear evidence of slow resolution and final disappearance of the shadow, whereas, if it is due to the reinfection type of disease, usually the shadow remains stationary much longer than in cases of the first infection type or actually shows evidence of increasing in extent or cavitation. If the lesion is of the first infection type, no symptoms appear beyond those of slight extent and of short duration about the time allergy is established; whereas in the reinfection type of disease, as the lesion progresses, symptoms, such

as fever, anorexia, and other manifestations of toxemia, make their appearance. Moreover, cough and expectoration are common symptoms in most lesions of this type. The age of the individual often helps in differentiating between the types of lesions, inasmuch as the reinfection type of chronic pulmonary disease is quite rare in infancy and childhood until the age of adolescence approaches.

Lesions of the reinfection type may be due to tubercle bacilli from exogenous or endogenous sources. Bacilli taken into the body through further exposure to tuberculous patients and finding lodgment on tissues already sensitized through the development of the first infection type of disease are met with a much more intense reaction on the part of the defense mechanism than those which bring about the first infection type of disease. The outpouring of neutrophiles quickly fixes the tubercle bacilli, following which large numbers of neutrophiles are destroyed. The second line of defense consists of monocytes. Unfortunately, tubercle bacilli are not destroyed as many other kinds of pathogenic organisms would be; they not only remain alive, but they may multiply. Thus, much tuberculoprotein is produced, and this has a destructive effect upon the adjacent tissues; thus necrosis results, and the necrotic tissue frequently finds its way into a ramification of a bronchus leaving as a cavity the space it formerly occupied.

Evidence is accruing to lead one to believe that the bacilli which result in the reinfection form of tuberculosis with its attending destruction are more frequently from the first infection foci than from exogenous sources. Sweany has shown that Nature may defeat her purpose. She first strongly imprisons tubercle bacilli of the first infection type of disease by laying down fibrous walls, calcium, and even true bone in some cases. These walls may suffice to keep the bacilli imprisoned throughout the normal span of life. However, Sweany has shown that these tubercle bacilli prisons may later be treated as foreign bodies, the walls resorbed, and bacilli set free upon allergic tissue. Again, trauma may result in the escape of bacilli from old first infection type of lesions. The defense mechanism is so powerful as to bring tubercle bacilli under control and imprison them temporarily in most children without any aid whatsoever by way of therapy. Indeed, no known therapy seems to be of any value. No matter how drastically we treat these lesions or how much we neglect or ignore them, they come under control in the same manner, but in both instances allergy remains, and the tubercle bacilli are not destroyed. In the case of the reinfection type of tuberculosis, however, treatment often becomes necessary because the defense mechanism is not capable of controlling the disease unaided; hence we resort to conservation of the energy of the body, collapse of the lung by artificial pneumothorax, extrapleural thoracoplasty, etc., in order to aid the defense mechanism.

I have never seen a patient experience the development of first infection type of tuberculosis more than once. Reinfections in persons who have had the first infection type of disease, when they lead to disease, are much more serious than first infections. The fact that the majority of persons (probably 80 per cent) who have the first infection type of tuberculosis as manifested by a positive tuberculin reaction do not develop reinfection forms of disease is in my opinion not due to any acquired resistance but to that defense mechanism present in the bodies of infants, children, and adults alike, which succeeds in imprisoning tubercle bacilli and keeping them imprisoned. In the minority (probably 20 per cent) of persons who develop the first infection type of tuberculosis, the period of time which elapses before the reinfection chronic type of disease appears is extremely variable; it may be a matter of a few months after allergy is established; more often it is a much longer period of time and in some cases forty years or more.

In my opinion, the first infection type of tuberculosis can never be looked upon as a protection against subsequent attacks of reinfection type of disease. In-

deed, it sets the stage for such attacks, first, by rendering the tissues allergic and, second, by harboring living and virulent tubercle bacilli for years, decades, or throughout the entire span of life. Just as long as the tubercle bacilli of first infection remain alive and virulent, they are definite liabilities to the body, and there is always the possibility that they may break prison at any moment and set up foci of reinfection type of tuberculosis, resulting in illness or even death. Therefore, I am unable to see any benefit whatsoever from the first infection type of tuberculosis, and the sooner physicians and others stop arguing in its favor the earlier will tuberculosis in the human family be controlled.

CHAIRMAN STEWART.—I shall ask Dr. McCordock to discuss the same question.

DR. McCORDOCK.—The problem of reinfection has been studied from many angles. Much of the work in this field has been devoted to a consideration of the relative probabilities of endogenous or exogenous reinfection in man, particularly in relation to the development of phthisis. The possibility of reinfection of the lungs from without is, of course, obvious. However, except in the case of children living in close contact with tuberculous individuals who have open cavities, it seems more likely that even secondary pulmonary infection is due to a spread of endogenous bacilli from the lesions laid down during primary infection. Experimental work, as well as pathologic study of human tuberculosis, clearly shows that the widespread inflammatory and caseous lesions characteristic of tuberculous pneumonia and other acute tuberculous processes are produced only by enormous numbers of bacilli, even in highly sensitized tissues. The usual external environment does not ordinarily offer the possibility of receiving such massive exogenous doses of tubercle bacilli as are necessary for the production of these secondary lesions. In the case of secondary tuberculosis of organs other than the lungs, such as pleurisy, peritonitis, and meningitis, it may be stated with certainty that these lesions are always due to endogenous bacilli. As far as the pathologic lesions and spread of the disease are concerned, it matters little whether reinfection is exogenous or endogenous, for the underlying principles are the same regardless of the source of the bacilli.

There is no question of the presence of living bacilli in many primary foci. They may be stained in old encapsulated foci, and their presence can also be demonstrated by animal inoculation when they are not found in stained sections. Of course, in some instances their presence cannot be revealed by any method, and in these cases the infection has been completely overcome.

The pathologic lesions of secondary infection are rather bewildering at first glance. However, any lesion, no matter how complex, can be separated into varying amounts of two basic types of reaction. Tissue reacts in two distinct ways to the presence of the tubercle bacillus. One type of reaction is the formation of a fibrous tubercle. This is the familiar tubercle of the textbooks, with its central giant cell, surrounded by epithelioid cells and lymphocytes, all held together in the form of a hard nodule by circumferentially arranged fibrous tissue. Because many of the cells comprising this tubercle are formed by the proliferation of tissue cells rather than by an exudation of cells from the blood stream, this type of tubercle is called a proliferative tubercle.

In contrast to the fibrous, proliferative tubercle there is another less familiar type which resembles a small abscess more than a tubercle. This is made up of a loose mass of large mononuclear cells which are very prone to undergo central necrosis and caseation, after which polymorphonuclear leucocytes invade the tubercle. Since this type of tubercle is produced principally by an exudation of cells from neighboring blood vessels, it is called an exudative tubercle.

Either type of tubercle can be reproduced experimentally by controlling the size of the infecting dose of bacilli. A few bacilli produce proliferative tubercles and large clumps of organisms the exudative type. In sensitized or allergic animals relatively fewer bacilli will call forth exudative tubercles than are necessary in the case of normal animals. In human lesions of the two types stained for bacilli, the proliferative tubercle contains so few organisms that they can be found only after long search while myriads of them abound in the exudative type. In allergic tissues the exudative type of reaction occurs more quickly than in normal tissues.

Many of the accidents which occur during the course of reinfection may be explained upon the basis of these two types of reaction. Acute exudative tuberculous pneumonia, involving one lobe or an entire lung, is usually the result of a soft caseous lesion rupturing into a large bronchus and flooding the lung with large numbers of bacilli, together with tuberculin-like material derived from dead bacilli. This accident is heralded clinically by a sudden onset of symptoms. Since the body is now sensitive to the bacillus and its products, the lung reacts quickly with an acute inflammatory exudate filling the alveoli and producing all the physical signs of consolidation. Constitutionally the body reacts to the absorption of tuberculin by fever, malaise, and prostration. The severity of the symptoms and the extent of the pneumonic consolidation will be directly proportional to the numbers of bacilli and the amount of their products discharged into the lung.

Similarly we may divide cases of miliary tuberculosis into two groups. Acute miliary tuberculosis, in which the organs are riddled with exudative tubercles, is always caused by the sudden discharge of many bacilli into a blood vessel from a caseous focus. Clinically the onset of this accident is abrupt with a chill and symptoms of a constitutional tuberculin reaction, which is not unlike the prostration observed in typhoid fever or some pyogenic infection.

In contrast to this acute type, miliary tuberculosis with proliferative tubercles comprises the vast majority of all cases. In these the development is so gradual that the onset cannot be determined clinically, and after death the tubercles are found to contain few bacilli. A large focus discharging bacilli into a blood vessel can never be found as in the acute cases, but one can always demonstrate microscopic involvement of blood vessels at the edge of active lesions. Through these tiny vessels bacilli in small numbers occasionally seep into the blood stream and form tubercles in distant organs. If the active lesion is large or if there are multiple lesions, more vessels are involved, and more tubercles are formed as a result. In this way all degrees of miliary dissemination may result, from a few scattered tubercles to intense studding of all organs.

In concluding, it remains for us to discuss acute inflammatory tuberculosis of serous cavities, the most frequent example of which is tuberculous meningitis. Meningitis is usually regarded as the prompt result of meningeal infection by way of the blood stream, occurring during the course of miliary tuberculosis. This belief is supported by the frequent association of miliary tuberculosis with meningitis, especially in children. The two are, however, not always associated. In the cases of acute miliary tuberculosis referred to, in which the viscera are riddled with many exudative tubercles, meningitis seldom develops. Furthermore, there are cases of meningitis without miliary tuberculosis. And finally, in those cases in which miliary tuberculosis and meningitis coexist, there is no constant relationship between the age of the meningeal exudate and that of the miliary tubercles in the viscera. In some the tubercles are older than the meningitis, and vice versa. These facts cast suspicion on miliary tuberculosis as the cause of meningitis. Since the exudate in tuberculous meningitis is of the exudative or inflammatory variety, great numbers of bacilli are necessary for its production. Enormous doses injected into the carotid artery in allergic animals never produce meningitis. It can be produced, however,

by trephining a hole in the skull and injecting the bacilli directly into the subarachnoid space. Because of these facts some local mechanism must be sought by which large numbers of bacilli can be discharged into the meninges.

An older caseous tubercle in the brain tissue, the result of an early primary dissemination, if it continues to grow after immunity becomes established, will eventually reach either the meningeal surface or the ventricular cavity. The discharge of the bacilli-laden caseous material from such a focus is comparable to the injection of bacteria into the subarachnoid space of animals. In 90 per cent of cases of meningitis in human beings such caseous foci discharging bacilli into the cerebrospinal fluid can be demonstrated.

What I have said of meningitis is also true of tuberculosis of other serous cavities. Pericarditis, peritonitis, pleurisy, and tuberculosis of joint cavities are all due to older caseous foci discharging bacilli into the cavity in question. This mechanism is in agreement with the facts and is certainly more logical than believing that in miliary tuberculosis the bacilli settle out in the meninges in one case and in the peritoneum, pericardium, or pleura, in others.

CHAIRMAN STEWART.—I gathered from what Dr. Myers said he lacks confidence in the immunity produced by first infection. I shall ask Dr. McCordock if he sees a relationship between primary lesions and occurrence in man of reinfection forms of tuberculosis.

DR. McCORDOCK.—During primary infection bacilli become disseminated; foci are laid down in distant organs; and the stage is thus set for the later development of the type of tuberculous lesions I have illustrated in the discussion of meningitis. The same mechanism occurs in other forms of acute tuberculosis.

CHAIRMAN STEWART.—Are these lesions in the brain a part of the primary complex, those that cause meningitis?

DR. McCORDOCK.—The caseous tubercles in the brain tissue which later rupture into the subarachnoid space and produce meningitis are formed during the period of primary infection by blood stream dissemination.

CHAIRMAN STEWART.—I shall ask Dr. Dienes to discuss the reaction to reinfection from the immunologic point of view.

DR. DIENES.—Long periods of clinical observation have afforded a great deal of evidence that in the previously uninfected child tuberculous infections even of a size to be readily demonstrable clinically or roentgenographically tend to heal without permanent impairment of health, whereas in the adult who retains from a previous infection some degree of acquired immunity, the development of lesions of equivalent extent results in the majority of cases in a fatal issue. This paradox is not specific to tuberculosis. In syphilis, the other major chronic disease of man, the conditions are similar. The primary lesion heals and leaves an immunity for life so that the patient on further exposure will not develop a primary lesion. He may die, however, of tertiary and metasyphilitic lesions.

At the present time, we cannot offer a real explanation of this paradox. But we have information on several points which are interesting and which indicate the way for further study of the problems involved. When a secondary lesion develops in an organism immune against artificial reinfection, it is certain that the immunity for some unknown cause has become temporarily or locally insufficient. This is not an hypothesis; the development of lesions by itself indicates that the immunity was insufficient. The first point which needs to be examined is whether the organism possesses really an appreciable immunity at the moment when the secondary lesions develop.

In man, we cannot test the immunity directly, but the pathologic characteristics of the secondary lesions, contrasted with those of the first infection, show clearly enough that the lesions develop in a relatively immune organism. The infection does not extend to the lymph nodes, and, if the lesions break down and bacteria are eliminated, they usually do not start new foci of infection.

Although we cannot say definitely why the immunity of the tissues breaks down, we can point out certain influences which favor this process. First of all, the secondary forms of tuberculosis develop more frequently under unfavorable hygienic conditions. Tuberculosis is mainly the disease of poor people. In central Europe the morbidity and mortality in tuberculosis were much higher during the Great War than before or later. When the general resistance of the population was lowered, the number of cases greatly increased. Intercurrent infectious diseases may break down the immunity. This point is strikingly illustrated by an observation recently described. The healed site of a vaccinia inoculation flared up and a new lesion developed in a child who contracted whooping cough. We know also, of course, the effect of trauma, pregnancy, and lactation.

The constitution of the individual probably plays an important rôle. This problem has been under discussion for a long time, but no definite conclusions could be reached until recently. A new and potentially fertile basis for the renewal of this discussion has been offered through the study of twins, a thorough study of tuberculous twins having been published recently from the Kaiser Wilhelm Institute for the study of heredity. By comparing the identical and nonidentical twins, the relative influences of constitution and environment can be determined. It was found that in identical twins, if one had tuberculosis, the other would also develop an active tuberculous process in 75 per cent of the cases. In nonidentical twins, if one was tuberculous, the other acquired the disease in only 25 per cent of the cases. These figures, if future work proves them to be correct, show definitely that the inherited constitution plays a considerable part in the development of secondary tuberculosis.

There is a marked similarity between the secondary forms of tuberculosis and certain infections with organisms of relatively low virulence, such as actinomycosis, different types of fungus infections, and lung abscesses. These conditions are not contagious, and, as far as can be determined by animal experiments, the causative microorganisms are nonvirulent or at most have only a slight virulence. In the case of lung abscesses it is known that the bacteria can get a foothold only if the resistance of the lungs is lowered. The abscess usually develops after other infections, or it is caused by a foreign body or septic embolus. Once the bacteria get a foothold, healing is slow or impossible, probably because noticeable lesions are produced only if the tissue is injured and unable to produce the normal defensive reaction. The extension of the lesions is contiguous following the injury to the tissues. The analogy with the diseases mentioned gives the best lead probably for the understanding of the slow healing and malignancy of the late forms of tuberculosis. In most cases the infection with tubercle bacilli starts a self-limited disease which heals after the development of immunity, leaving a small residual lesion. The immunity mechanism usually functions satisfactorily. The immunity resulting from the first infection is subject to oscillations both generally and locally in certain organs, and the late forms of tuberculosis develop only if the immunity is lowered below a certain point. This occurs only in the minority of infected human persons. The healing is slow probably for the same reasons as in a lung abscess. Large areas of injured tissues are present, and the influences which lowered the immunity persist.

The conditions under which tuberculous lesions heal give further support to this conception. After many years of experimentation it has become apparent that specific therapy is of little value probably because most patients have as much specific immunity as the organism is able to produce. The healing is favored by

procedures which increase the normal functioning of the defensive forces: good hygiene, rest, and immobilization of the lesions. From these observations many draw the conclusion that the specific immunity is not important in tuberculosis. I do not believe that this conclusion is justified. The healing of the first infection indicates sufficiently the importance of specific immunity. The observations concerning the healing of tuberculous lesions rather indicate that in the presence of specific immunity the development and healing of secondary lesions depend on the local condition in the tissue where the lesions develop. I have mentioned previously that in animals the influence of local tissue on the tuberculous lesion is quite apparent.

From the immunologic point of view there seem to be important differences between the first infection lesions and the late forms of tuberculosis. In the first infection the normal defensive forces of the organism function satisfactorily, but they are not able to prevent the establishment and spread of infection. When the specific immunity develops sufficiently in the presence of normally functioning tissue, the spread of infection is checked and the lesions heal. This course may be influenced by overwhelming infection or by other conditions which hinder the normal functioning of the defensive reactions. In secondary tuberculosis specific immunity is usually present or develops in a short time. Lesions develop only when for some reason the normal activity of the defensive forces is hindered, and for this reason the specific immunity cannot bring about the healing of the lesions. The healing depends on the slow restoration of the normal activity of the defensive forces. The extensive areas of impaired tissue constitute a serious difficulty.

I wish to say a few words concerning allergy, which has played a considerable part in the discussion of the pathology and healing of tuberculous lesions. It is believed that allergy is dangerous because it transforms the protein substances of tubercle bacilli into a violent poison and helps to break down the resistance of the tissues. I do not believe that there is definite proof to support this conception.

The tuberculin sensitiveness represents, as I have previously explained, the development of an active immunity process. We know that the immunity reactions under artificial conditions may be dangerous. Patients have been killed by testing for allergy; the small doses of antigens made use of in the tests in the presence of certain types of antibodies were sufficient to cause death, yet no one would for this reason advise the suppression of antibody production.

The breaking down of tissues which are exposed to the effect of tubercle bacilli cannot be attributed solely to allergy. Necrosis in tuberculin reactions is an artificial phenomenon which probably has no exact equivalent in the course of the natural disease. In order to produce necrosis even in a very sensitive organism, the doses of bacteria must be so large that they cannot be disseminated during the disease. In experimental work if the dose of bacteria is kept small, within the limits which might reasonably be involved in the spontaneous disease; the most remarkable effect of tuberculin sensitiveness is a strong infiltration of the tissue with mononuclear cells and the accelerated formation of tubercles. This type of response is characteristic of the active phase of immunity, and it is present just as regularly in animals sensitive to egg white as in tuberculous animals. Direct observation shows that this tissue reaction has an important part in the resistance to the infection. In the experiments of Lurie, to which I have previously referred, the bacteria intravenously injected into highly immune rabbits were enclosed in small accumulations of mononuclear cells. There they were destroyed, and the tiny nodules disappeared in a few days. If the immunity was less strong, the bacteria were not destroyed so soon, and tubercles were formed. They developed much more quickly than in nonimmune animals, and they were absorbed soon after the bacteria were destroyed in them.

To my mind, the most important effect of allergy as it occurs in the spontaneous disease is not the production of destructive lesions but the acceleration of tubercle formation. The immunologic significance of this process is apparent in the experiments.

Dr. Myers referred to the formation of tubercles as "normal" response of the organism, contrasted with the "specific" immunity response, and compared it to the tissue reaction to silica. My opinion differs in this point from this widely accepted opinion; I believe that the formation of tubercles and, in general, of the infectious granulomas and foreign body tubercles depends on an entirely different mechanism. The lesions show remarkable similarity in various diseases caused by widely different organisms such as the virus of lymphogranulomatosis, *B. typhosus, B. abortus,* different fungi, etc. In all these cases strong tuberculin type of hypersensitiveness develops, and as mentioned above it is probably responsible for the tissue reaction. The microorganisms do not seem to have any characteristic chemical or physical properties in common, and most of them are not especially resistant. In specific immunity the type of response is often not characteristic but is produced under conditions different from those under which it would be produced in a normal organism. The tissue response in tuberculosis, according to my observations, depends to a large extent on the immunity response and indicates the early development and importance of this process.

Allergy also produces exudative phenomena, and I agree with Dr. McCordock concerning the pathologic effect of this process. In tuberculosis, however, under natural conditions this increased inflammatory reaction does not seem to result in tissue destruction. It is not known how far allergy is responsible for caseation, but caseation is certainly not a purely allergic phenomenon.

CHAIRMAN STEWART.—Do I understand correctly that in order to gain maximum benefit from acquired immunity you have to stay in optimum general conditions?

DR. DIENES.—I believe so.

CHAIRMAN STEWART.—Does the first infection introduce a susceptibility to phthisis into the race?

DR. DIENES.—The answer depends on what we mean by susceptibility. The first infection is an introductory step in the development of phthisis, but we have no reason to believe that it is the cause of the malignancy of the disease. A person who develops phthisis under similar conditions but without the protective influence of the first infection probably would contract a more rapid form of tuberculosis. This rapidly fatal development of the disease is observed in primitive peoples. The first infection creates both an advantage and a liability. It depends on how frequently a person is exposed to infection, whether the resistance produced by the first infection is more valuable than the danger created by the continuous presence of tubercle bacilli in the organism. In present-day conditions, the majority of the population is rarely exposed to infection, and the liability created by the first infection probably overweighs its usefulness.

CHAIRMAN STEWART.—What perpetuates tuberculosis in man?

DR. DIENES.—Certainly the persons with open pulmonary lesions.

CHAIRMAN STEWART.—Dr. McCordock, do you think the acquired immunity compensates for the risk that resides in primary lesions?

DR. McCORDOCK.—In the vast majority of children, as I have already pointed out, the primary infection is arrested without any risk, for these individuals develop

an encapsulated fibrous or calcified primary complex without an extensive dissemination of tubercles to other organs. This large group of individuals is able to live in urban communities and survive occasional exposure to tubercle bacilli without again contracting the disease. In the light of this fact, the immunity produced in the majority of all individuals by a primary infection seems to justify the risk of fatal tuberculous disease in a small percentage of all children infected by natural means.

CHAIRMAN STEWART.—What does the first infection prevent? Does it prevent consumption in bone, in joints, or meningitis?

DR. McCORDOCK.—I do not think it prevents them in all the cases, but it certainly does in the vast majority of instances. I am a firm believer in the size of the initial infecting dose, or rather in the number of bacilli that lodge at one point; whether the large numbers are due to an original infection or are produced by the multiplication of a small one, the results are the same. Those who during childhood have large numbers of bacilli concentrated at one point in the lung are the individuals destined to develop either progressive secondary lung lesions almost immediately following primary infection, or some acute tuberculous process due to foci of infection laid down during the primary phase of the disease. For this smaller group, the first infection does not, of course, prevent serious secondary infection.

CHAIRMAN STEWART.—You feel that the immunity outweighs the hazard that also goes into it? So it is not a simple immunity; there is a hazard to it?

DR. McCORDOCK.—There is of course a hazard to any infection; that is the price one must pay for immunity. In the human subject, immunity to tuberculosis can be achieved only through infection.

CHAIRMAN STEWART.—After considering the information presented here, combined with other information at your disposal relative to the immediate and future potential effects of specific immunization with heat-killed bacilli or attenuated organisms, such as B. C. G., do you think immunization of children is in the experimental stage and from a scientific standpoint should be considered that way rather than to be offered to the public as a method of preventing tuberculosis?

DR. McCORDOCK.—Although a natural immunity is possessed by various animals for certain strains of the tubercle bacillus, as far as the human species is concerned no useful natural immunity exists for either the human or bovine strains. All races are susceptible to at least one strain. In most individuals primary infection produces a resistance which is well-nigh complete, and the disease is arrested. However, all immunity is relative, and a sufficiently large dose of virulent organisms will break down any immunity and produce active disease.

At the present time, it is almost utopian to hope for a civilization from which the tubercle bacillus can be banished. Evolutionary processes may gradually weed out those individuals whose immunologic defense mechanisms are not able, even after slight primary infection, to arrest the disease, and in the end only those in whom parasitic adaptation is possible will survive. In the meantime, I think we should proceed cautiously with wholesale inoculations of live organisms. My experimental experience with B. C. G. and other types of attenuated bacilli does not make me enthusiastic about the use of these strains for prophylactic inoculation in children.

Since primary infection inevitably occurs in the large majority of individuals, it seems logical, theoretically at least, to vaccinate infants under conditions so controlled that only localized lesions will be produced. In practice, however, actual experience is not yet sufficient to control all of these conditions. If it were pos-

sible to induce a high degree of immunity by vaccination without at the same time producing exquisite sensitization of the tissues, such protection would be an improvement upon that resulting from natural infection, for the most distressing symptoms and many of the destructive results of secondary infection are due to allergic manifestations.

If protective vaccination must be resorted to, dead bacilli should be used. A moderate degree of immunity may be produced in animals by the inoculation of dead bacilli. This results in some prolongation of life when such animals are later injected with live organisms. While such immunity is slight and could never take the place of that developed by natural infection, it might nevertheless be an advantage to anticipate primary infection with the mild immunity that these dead organisms produce.

CHAIRMAN STEWART.—I shall ask Dr. H. C. Stewart whether he believes the effects of first infection provide a satisfactory solution for our tuberculosis problem.

DR. H. C. STEWART.—This question is one which cannot be answered at this time. There are many things to be considered. From an epidemiologic viewpoint tuberculosis is a communicable disease. This disease, however, offers many points of difference from those illnesses usually considered in the class of communicable diseases. Our present knowledge offers no exact analogies between tuberculosis and other communicable diseases. It is true, of course, that infection with the tubercle bacillus must precede the development of a tuberculous process within the human body. The course of events subsequent to the lodgment of the tubercle bacillus is evidently influenced by a multiplicity of factors. Obviously, if infection could be prevented, the disease would of necessity disappear. It can scarcely be hoped that this freedom from infection can be obtained, however much it might be desired. There remains the study of the circumstances and factors which influence the course of events after the tubercle bacillus has entered the body.

One of the chief factors appears to be that of contact with individuals discharging tubercle bacilli. There seem to be differences of opinion as to whether persons having had a first infection subsequently develop the destructive type of tuberculosis as the result of an added infection from outside the body or whether this destructive process is the result of changes at the site of the earlier infection without an added infection from outside the body. It is not necessary that one of these conditions be held true to the exclusion of the other possibility. The factor of contact is measurable to some extent, and further studies of contact in connection with the development of clinical tuberculosis seem necessary.

Another factor to be considered is that of resistance on the part of the host to the development of tuberculosis which becomes clinically recognizable. While resistance of this type cannot be measured, the probability of its existence must be recognized. The history of tuberculosis in a population not previously acquainted with the disease is quite suggestive of a lack of resistance. Studies now under way may serve to give additional information concerning the factor of resistance.

Carefully collected and detailed information as to the course of events from infection over a number of years will give information which may allow a clearer understanding of the later effect of a naturally acquired first infection. At present the information available does not seem to provide an answer to this question.

CHAIRMAN STEWART.—Could I ask a question at this point? Does a decline in the infection rate parallel a decline in the death rate?

DR. H. C. STEWART.—It is reasonable to believe that with a decline in the tuberculosis death rate there should also be a decline in the infection rate. This is based on the belief that there is a decreasing number of cases of the severe type of

tuberculosis which contribute largely to the death records and which are more likely to be important sources of infection for other individuals. There is some evidence at hand which shows that there is a low rate of infection, as judged by the tuberculin reaction, in the younger age groups in parts of the country which have low tuberculosis death rates.

CHAIRMAN STEWART.—Do you think, then, that if we sustain the present prevalence of acquired immunity, we benefit less than if we decrease it in the population in general?

DR. H. C. STEWART.—That question is one which probably cannot be satisfactorily answered at the present time. It is necessary that more be known as to the possible immunizing effect of naturally acquired infections. More should be known as to the development of destructive types of tuberculosis in adult life of those who have been infected in childhood, and those who have not.

CHAIRMAN STEWART.—Dr. McCordock, on considering the immediate and future potential effects of maintaining or increasing the prevalence in the population of specific immunologic changes and foci of disease by permitting human contact infection, do you think we can control our tuberculosis problem by keeping the infection going?

DR. McCORDOCK.—I do not think we have any choice in the matter. It will be a long time before we can get rid of the tubercle bacillus; indeed, it will require a much longer time to accomplish this than the twenty-five-year period suggested for testing out the B. C. G. vaccine. As long as the tubercle bacillus is present in our civilization, chance contact infection cannot be effectively prevented.

In view of this fact it does not seem advisable to prevent children from acquiring small protective doses of bacilli early in life. If safeguards are established to prevent primary infection during childhood, the same sequence of events will later follow first infection when it occurs during adult years. Every effort, of course, should be made to prevent individuals with open pulmonary cavities from coming into intimate contact with children of any age, or with adults for that matter. However, protection from such massive doses of bacilli will not prevent the development of the usual small foci produced by the chance inhalation of the few organisms necessary for an immunizing dose.

CHAIRMAN STEWART.—Dr. McCordock, do you think it is safe to prevent the infection?

DR. McCORDOCK.—If the individual who has never received a primary infection could subsequently be protected from chance contact with tubercle bacilli, it would be perfectly safe, but at present this is not possible in all communities.

A great deal has been written about the severity of primary tuberculosis in primitive peoples, reared in an atmosphere free from tuberculosis, when they come in contact with civilization. Borrel's reports on the ravages of first infection among the Senegalese troops brought to France during the World War confirm all these earlier studies. More convincing evidence of this fact was recorded by Aschoff, who found acute fatal primary tuberculosis of the childhood type in troops from the tubercle-free Anatolian mountain villages. In many autopsies he never found the slightest evidence of an old juvenile first infection. These people had been spared a primary childhood infection, and no doubt would have been perfectly safe had they remained shielded in their native mountain communities.

It is unfortunate that in acquiring an immunity some individuals must succumb to the effects of the first infection. This may be regarded as a weeding-out process. Is it not better for this weeding to occur during the early years of life than to defer it until productive years are reached?

CHAIRMAN STEWART.—Dr. H. C. Stewart, after considering the information presented here, combined with other information at your disposal relative to the immediate and future potential effects of specific immunization with heat-killed bacilli or attenuated organisms such as B. C. G., do you think immunization of children is in the experimental state and from a scientific standpoint should be considered as such rather than to be offered to the public as a method of preventing tuberculosis?

DR. H. C. STEWART.—If it can be shown definitely that naturally acquired infections confer immunity which is lasting, then the possibility of widespread use of such artificial immunization should be considered. If, on the other hand, there is a higher incidence of severe types of tuberculosis and deaths in those individuals who have acquired an infection in childhood when comparison is made with those individuals who have not, taking into consideration such factors as contact, then the attempt to produce artificial immunization is useless. Until additional information as to these points is at hand, it would not be reasonable to offer so-called artificial immunization as a method of preventing tuberculosis.

CHAIRMAN STEWART.—I shall ask Dr. Myers to discuss this same general topic.

DR. MYERS.—The time has long since passed when we inhale or ingest tubercle bacilli daily, weekly, or monthly. In the University of Minnesota, where we have approximately 12,000 students, we have found that only 25 per cent of the entering freshmen react positively to the tuberculin test at the age of about twenty. That means if the same condition continues, it would take eighty years before all of those individuals would be infected for the first time. Therefore, the likelihood of reinfection is not so very great. In the School of Education, we have found that there is an annual increase in positive reactors of only 1 per cent.

The method of attempting to immunize human beings against tuberculosis with heat-killed bacilli or attenuated organisms, such as B. C. G., does not seem to me to offer a satisfactory solution of the tuberculosis problem. The use of heat-killed bacilli probably brings about only temporary changes in the body. No information is available to prove that this method would be at all effective in preventing tuberculosis in human beings. The use of B. C. G. in my opinion is even a more questionable and possibly dangerous procedure because of the introduction of living tubercle bacilli in large numbers in the human body. It not only results in sensitizing the tissues to tuberculoprotein, but first-class bacteriologists claim to have actually caused it to regain its virulence. Already a large experiment with B. C. G. is in progress, these bacilli having been introduced into the bodies of more than a million human beings, mostly infants and children. It is a well-known fact that even virulent tubercle bacilli cause very little destruction during the period of childhood and, except for the relatively small number of infants and young children who develop reinfection forms of disease, such as meningitis, miliary tuberculosis, and tuberculous pneumonia, the tuberculosis problem in childhood is not at all serious when compared with the problem beginning about the period of adolescence and continuing throughout the span of life. What effect these avirulent microorganisms introduced into the bodies of infants and children will have upon the disease in adult life has not yet been determined, and very little will be known about it for at least another quarter of a century. While waiting for this period to elapse, we can, by a proved method of control, namely, preventing contact of infants and children with persons who have the disease in a communicable form, reduce tuberculosis to a disease of minor significance in the United States.

By advocating and insisting upon universal infection of our children through permitting contact with tuberculous patients or taking dairy products containing

living bovine type of tubercle bacilli in order to have them receive a so-called protective dose of tubercle bacilli, we would set the clock of tuberculosis back at least a century, when probably well-nigh 100 per cent of the children became contaminated with tubercle bacilli and when the mortality rate from tuberculosis among persons of all ages was 450 per 100,000 population. We would bring about situations in many parts of the United States now relatively free from tuberculosis, which would be comparable to those of some sections of Philadelphia, where 90 per cent of the young adults react positively to the tuberculin test and where the mortality from tuberculosis is extremely high as compared with other parts of the country; or we would quickly throw upon our nation a problem not unlike that of a few other nations or the Island of Puerto Rico, where a high mortality rate exists. There is good evidence that the mortality and morbidity curves run almost parallel with the incidence of infection curve. The lower the incidence of infection in any community, the lower the morbidity and the mortality rates; it is only the infected who develop clinical tuberculosis. The liabilities of first infection with tubercle bacilli through human contact far outweigh every possible asset.

The veterinarians and closely allied groups of this country have demonstrated a most excellent method of control. They have not depended upon immunity developed through contact because they early learned that it is inadequate. They were cognizant of the fact that such a method was of no avail because it had had ample opportunity to demonstrate its value in the cattle herds before the present method of control was undertaken. Here and there they attempted to immunize cattle by various methods, including B. C. G., but found no effective method. As early as 1891, a small group of veterinarians manifested great confidence in the specificity of the tuberculin test in screening tuberculous cattle from the herds; they were bitterly opposed by others who did not have a clear vision or did not understand the nature of the test. This small group with a true knowledge of tuberculosis and a clear vision of its control insisted upon slaughter of every animal that reacted positively to the test, no matter how healthy in appearance or how valuable; they considered every such animal a potential reservoir of tubercle bacilli. Here, again, they were bitterly opposed, and their work was retarded by those who were uninformed or misinformed, and those to whom the tuberculosis problem among cattle had not become transparent. The result is that with the exception of three small sections of the United States, the cattle herds of America have been accredited and in some whole counties the disease has been completely eradicated from the entire cattle population. The solution of the veterinarian's problem has in no small way aided in the solution of the tuberculosis problem in the human family. This, together with the pasteurization of dairy products, has materially reduced the incidence of positive tuberculin reactors among human beings, as well as the incidence of certain forms of tuberculosis, such as that of the cervical lymph nodes, bones, and joints, etc. Indeed, we can almost say that the veterinarian has helped us more than we have helped ourselves. By adopting the veterinarian's method so far as possible and substituting isolation, treatment, and education for slaughter, we are able to quickly reduce the tuberculosis problem in any community in a short period of time. For example, Boynton has shown that in one state where this method has been in effect in only a small way the mortality from tuberculosis among infants decreased 88 per cent between 1915 and 1933. Had the method been carried out to its logical conclusion, as the veterinarian carried out his method, the mortality by 1933 might have been nil.

I have in mind a county where for approximately ten years tuberculin testing has been used to screen out those persons who should have careful examinations for tuberculosis and where the communicable cases have been isolated or treated to make them safe associates, with the result that now only 4.2 per cent of the children,

including those of high school age, of that county react positively to the tuberculin test. By continuing the search for any newly developing cases of communicable tuberculosis and controlling it, it is obvious that the time is not far distant when among the children of that county the positive tuberculin reactor will be a rarity.

The belief is often expressed that, when that time comes and the children pass into adult life uninfected with tubercle bacilli, should they then become infected, they will fall prey to a very severe, highly fatal form of tuberculosis. This belief has been completely exploded through recent observations of uninfected adults, who were observed to have become infected as students of nursing and medicine and who were seen to develop not the rapidly progressive, highly fatal forms of tuberculosis but that extremely benign first infection type of disease which develops when infection first occurs in infancy and childhood.

Therefore, the longer the first infection type of tuberculosis can be prevented from developing in the human body, through avoiding exposure, the better. Already by isolation or treatment of persons with the disease in communicable form we have made it possible in many sections of this country for the majority of persons to pass into adult life without having developed a primary tuberculosis complex. Indeed, where one or two decades ago we said that 90 to 95 per cent of the children had been infected with tubercle bacilli by the age of fifteen years, we are now able to state on the basis of actual tuberculin testing that 90 to 95 per cent of the children have been adequately protected against infection with tubercle bacilli. If our present program of control is intensified, there is every reason to believe that we will be able to extend this low incidence of infected persons into later adult life and finally reach the ultimate goal when human beings will be able to pass through the entire span of life with very few having been contaminated with tubercle bacilli.

CHAIRMAN STEWART.—Will Dr. Dienes also discuss this same general topic.

DR. DIENES.—I believe that the final solution of the tuberculosis problem is the prevention of the infection and the elimination of the disease. I do not see why this should be impossible in the not very distant future. We know of native people who in the surroundings to which they were well adapted did not have tuberculosis. I hope that with scientific methods we shall be able to adjust ourselves as successfully to our living conditions as the Eskimos or African natives are adapted to their environment.

CHAIRMAN STEWART.—Dr. Dienes, how many years do you think we shall have to study B. C. G. before we will know its true value?

DR. DIENES.—I believe you will have to study it for at least twenty-five years. This much time is necessary to follow the development of vaccinated children.

CHAIRMAN STEWART.—Would you keep it as an experimental problem rather than offer it to the public?

DR. DIENES.—I believe that it is still an experimental problem and that it should be used only under conditions which permit the scientific evaluation of the result. I should like to add that no striking results have been obtained in the eradication of tuberculosis in cattle by vaccination.

I have been very much impressed by the work of Dr. Myers and Dr. Stewart. By the observation of a large number of healthy children, they were able to establish the clinical course of the first infection with tubercle bacilli, and at present they have begun to accumulate observations concerning the antecedents of the secondary forms of tuberculosis. In tuberculosis and in many other diseases this method, which consists of the observation of a large number of seemingly healthy persons through a long period of time, seems to be the only way of obtaining information

about the influences which prepare the development of the disease. We have to observe and to record these influences as exactly as the symptoms of the disease; otherwise we shall never have information concerning their importance. Appropriate institutions able to carry out similar work in sufficiently large scale and in sufficiently detailed form do not exist, and I wish to emphasize that in many important problems of public health probably the organization of such institutions would be the most important step forward.

Concluding Remarks

Chairman Stewart.—Evidence presented in this discussion indicates that children customarily resist and control naturally acquired infection with virulent tubercle bacilli in a remarkably satisfactory manner. Although a susceptibility to infection is universally present, nevertheless previously uncontaminated children obviously are not hopelessly at the mercy of the tubercle bacillus. Apparently readily available native resources which can quickly produce a very dependable defense reaction are generally present in the tissues of young uninfected individuals. These native resources from which the complex postinfection reactive changes are derived probably can be designated tentatively as natural resistance or native defense potentialities. From a practical point of view, this mechanism functions in a very satisfactory manner. This deduction is based on the observed relative infrequency with which serious illness and death accompany or immediately follow the transition from the uninfected to the infected condition.

One of the important weaknesses of normal resistance is its inability to prevent infection. Additional defects theoretically attributable to this preinfection state probably relate mainly to the apparent ineffectiveness with which previously unaltered tissues control some of the early changes which occur during the postinfection interval that precedes the development of a specific immune response. It is during this relatively short interval that the invading organisms probably multiply with exceptional rapidity and also exhibit an ability to escape quite freely from the site of their initial implantation to produce multiple subsidiary foci of disease. Instead of preventing the occurrence of changes of this character, infection with virulent tubercle bacilli obviously initiates their development. The subsequently created immune reaction apparently curtails each of these activities of the tubercle bacillus, and it also appears to make the body somewhat refractory to exogenous reinfection. In these respects the postinfection state seems to be superior to the preinfection state of the tissues.

Fortunately the apparent inferiority of the latter does not seem to be a very serious one. The relative infrequency with which serious immediate consequences accompany the transition from the uninfected to the infected condition supports this belief. Apparently no urgent reasons exist for attempting to correct the inherent defects of normal resistance at least by permitting infection with virulent tubercle bacilli to occur.

The degree to which the response to tuberculous infection is either nonspecific or immunologically specific, and the relative importance of the influence of each of these two types of reaction in determining the course of the disease, probably cannot be accurately stated at the present time. Although the specific immune response seems to dominate the situation shortly after bacilli enter the body, nevertheless the possibility remains that relatively inconspicuous nonspecific changes may simultaneously continue to serve important and sustained functions which also contribute to the control of the disease. Apparently there is no evidence that these two defensive forces are mutually exclusive or entirely antagonistic.

If the effects of infection with virulent tubercle bacilli were limited to the correction of inherent temporary defects of natural resistance by merely creating an

acquired relative immunity, the benefits ordinarily attributed to a contamination of this character probably would not be seriously questioned. The simultaneous production, however, of multiple foci of disease in which virulent bacilli often survive for years, and the unexplained but observed frequent failure of the acquired immunity to prevent these surviving organisms from ultimately causing serious secondary forms of tuberculosis constitute factors which undermine confidence in the value and safety of the combined pathologic and immunologic postinfection state and create doubts relative to its definite superiority over the normal and customarily adequate preinfection condition of the body.

The universal presence of many tuberculin-sensitive but otherwise apparently healthy children demonstrates the general prevalence in the child population of an inherent ability to resist and to survive the deleterious effects of naturally acquired or accidental infection. These survivors have demonstrated a native capacity to control tuberculous infection in a satisfactory manner so far as escaping serious illness and death are concerned, but what they have actually gained by making this demonstration merits consideration. Apparently a state of being relatively refractory to exogenous infection has been added to their previous ability to control an infection. They also seem to have acquired an increased capacity to curb the reproductive and migratory tendencies of the invading organism. In exchange for these apparent benefits, these survivors incurred the risks which immediately attend an infection with virulent tubercle bacilli, and they also face the future greater danger that organisms persisting in foci of disease may eventually escape and produce serious secondary forms of tuberculosis.

The failure of the acquired immunity to destroy all of the invading bacilli and the uncertainty that it will control the activities of the surviving organism throughout the postinfection span of human life provide excellent reasons for avoiding unqualified statements to the effect that the customarily satisfactory postinfection state is superior to the generally dependable preinfection state of the body. An inclusive statement of this character obviously does not apply to all of the effects of infection with virulent tubercle bacilli.

The observed severity of tuberculosis following its introduction into previously uncontaminated races is generally attributed mainly to an antecedent absence of a specifically protective immunity. Whether this commonly accepted explanation for an observed fact is valid or not probably can be determined in time by noting the future fate of the cattle in the United States with respect to tuberculosis. The alleged protective influence of a specific relative immunity has been generally removed from the herds in this country, but in spite of this change apparently no alarming outbreak of the disease has occurred among these nonimmune animals. This extensive animal experiment tentatively indicates that no serious immediate results attend a wholesale elimination of a specific relative immunity to tuberculosis and suggests that the apparent inferior ability to resist tuberculosis displayed by previously uncontaminated races may not be mainly due to a general absence of an acquired relative immunity.

A general consideration of a somewhat paradoxical situation leads the chairman of the panel discussion to favor the view that the normal state of the uncontaminated body is superior to the combined immunologic and pathologic postinfection state. This conclusion reflects a conviction that the protection benefits derived from an infection with virulent tubercle bacilli are not commensurate with the liabilities simultaneously created. The chairman is also of the opinion that no dire results in the form of epidemic recrudescences of tuberculosis will follow a general elimination from the human race of a naturally acquired specific relative immunity to tuberculosis.

This discussion probably has focused attention on several important questions which merit a continuation of scientific scrutiny and debate. In this respect it has served its purpose.

Academy News

The meeting of Region I of the American Academy of Pediatrics will be held in Boston, November 12 and 13, 1937.

Dr. Donald Woods, San Diego, Calif., died of a brain tumor on December 10, 1936.

Dr. Thomas DeWitt Gordon, Grand Rapids, Mich., died of coronary thrombosis on November 20, 1936.

Dr. Paul W. Beaven, Rochester, N. Y., has been made cochairman for New York to replace Dr. E. J. Wynkoop, Syracuse.

Book Reviews

Practice of Pediatrics. By Various Authors. Edited by Joseph Brennemann, M.D. 4 Volumes With Index Volume, 1937. W. F. Prior Company, Inc., Hagerstown, Md., Price, $63.

The appearance of a new pediatric System is a publishing event of major importance. It is even more, as willy-nilly it is inherently a vivid cross-section of the level of contemporary American pediatrics. Looking upon the result as a whole, the reviewer feels that the editor, Dr. Brennemann, may take an honest pride in a job well done and that the material reflects the rapid development of pediatrics in recent years. Beyond question a large proportion of the contributions are outstanding in character.

The whole idea of a System raises certain questions in regard to the purpose and scope. On one hand, we may consider the function of a System chiefly that of a work of reference, something to be referred to in order to gain a quick answer to some moot point, therapeutic measure, or the like, containing a bibliography which enables the reader to dig deeper if he desires. We might term this the encyclopedic viewpoint—a System built up of a series of critical reviews—a plan and method of presentation characteristically Teutonic in its derivation. On the other hand, we may conceive of a System as a series or group of articles in which the subjects are discussed from a more limited personal point of view, by individuals who by their experience and connection or work with the specific topic may be regarded as having the right to have their opinions looked upon as more or less authoritative. It is by contrast a method or plan English in its derivation. Each has its weak as well as its valuable points. The first usually results in a rather dry uninspiring collection of articles but has its use in saving perhaps hours of time to the busy pediatrician or student. The second method requires a more careful and judicious selection of authors and gives a more readable and interesting text and, in the ultimate analysis, probably a more valuable group of articles. A reviewer must hold this distinction clearly in mind in attempting to estimate the value of a System.

Dr. Brennemann in his introduction, and in the unusually large number of chapters he has himself contributed, has made it clear and distinct that, in editing and planning the System and in his selection of authors, he has had the second purpose in view. It is from this viewpoint therefore that "Brennemann's System" must be judged. If the reader expects to find detailed reference to every etiologic or therapeutic problem or opinion, for example, with extensive references, he will be disappointed. The weakness of this method of building up a System lies in the limitation of the discussion of the topics to the personal experience and opinion of the author. This may be illustrated by the chapter, "Chorea" by Gibson—we are not singling out this chapter for adverse criticism but simply are referring to it in order to illustrate a point. Under the treatment of chorea he gives a considerable space to the use of nirvanol, while fever therapy by vaccines (other methods of producing hyperpyrexia are not mentioned) is brusquely cast aside. Thus the method of choice of the author is stressed, and methods preferred and used by others are inadequately discussed. An uninformed reader may obtain a quite erroneous impression of general American pediatric practice.

It is not the function of the reviewer to pass judgment on the superiority of one method of constructing or planning the System over the other, but simply to point

out the method which the editor has selected and by which the System in all fairness must be judged, for, if it were to be judged from an encyclopedic viewpoint, the answer would be that it is a failure. As a whole, the authors have held quite closely to Dr. Brennemann's intent; this is particularly true of the pediatricians who have contributed. A number of the authors in affiliated fields, such as surgery, have written articles rather monographic in character, which fact brings a certain amount of unevenness to the System, and they have occasionally been allowed space out of proportion to the importance of their specific topic when it is considered in relation to the whole. One can sympathize with the difficulties of an editor who has to deal with a large number of authors who from their personal interest in some special field or topic naturally tend to focus on the detail of a part rather than the picture as a whole.

The editor has selected a group of 119 collaborators, of whom approximately 60 per cent are from the field of pediatrics and the remainder are from the affiliated fields of psychology, surgery, and the like. As a whole, he is to be congratulated on his choice of authors, and in many instances the choice for the particular subject is the first name that comes to the mind of anyone familiar with American pediatrics. More exceptions are found in the group of authors of affiliated subjects, but here too are many instances of ideal selection. A reviewer or reader will find numerous points of differences between his personal viewpoint and the viewpoint expressed by some of the authors, and such differences will vary naturally with the individual reviewer or reader. A discussion of such points is not germane criticism since it simply represents differences in personal opinion and experience. With these general statements in mind a more detailed review of the individual volumes may be made.

Volume I, composed of forty-three chapters, contains what might be termed basic material, and parts of it will be of more interest to the pediatrician than to the general practitioner. After "History of Pediatrics" by Isaac Abt there is the excellent "Introduction to Pediatrics" by Blackfan. The important subject, "Heredity and Environment," is ably discussed by H. S. Jennings. Washburn contributes a well-balanced chapter, "Appraisal of Healthy Growth." "Mental Growth in Infancy" by Gesell, and "Mental Hygiene" by Esther Richards in this volume, together with the chapter, "Psychopathology," by Kanner in Volume IV, form a splendid group of articles written by individuals fully cognizant of pediatric needs. The chapter, "Puberty and Adolescence," by B. Sachs is a reiteration of the author's pet aversions rather than an adequate discussion of the subject. "Temperature Regulation" and "Basal Metabolism" by Talbot are sound and excellent summaries. The chapters, "Examination of the Child" and "Treatment in Childhood," are contributed by the editor, and treatment is further continued by the chapters, "Blood Transfusion," by Powers and "Parenteral Fluids" by Hartmann. The chapter on the hygiene of infancy and childhood is contributed by Richard Smith. The remainder of the volume is more clinical in nature. Brennemann's chapters on infant feeding are perhaps the most personal in the System. The editor further discusses the minor nutritional and digestive disturbances of infancy while the more serious types of disturbances are ably discussed by the late Dr. Marriott. The vitamins and avitaminoses in general are discussed by Tisdall, and this discussion is followed by the specific chapters, "Pellagra" by Weston, "Scurvy" by McIntosh, and "Rickets" by Martha Eliot and Park. The volume closes with chapters on the newborn by Grulee and Bonar, and on premature infants by Julius Hess. Regarded as a whole this volume appeals to the reviewer as the best in the System, and most of the chapters can be read with profit by the most experienced pediatrician.

Volume II (fifty-nine chapters) is devoted chiefly to the infectious diseases and diseases of the respiratory tract. The introductory chapter, "General Aspects of

Infection and Resistance'' by Rivers, is one of the outstanding chapters in the System. Thirty-four chapters are then given to the consideration of specific diseases, including ''Diphtheria'' by Schick, ''Poliomyelitis'' by McKhann and Wilson, ''Syphilis'' by Jeans, ''Typhoid'' by the Abts, ''Scarlet Fever'' by Toomey, and ''Tuberculosis'' by Stewart. In most of these the material is adequately treated although the allotted space seems at times disproportionate. Thus eighteen pages are given to the discussion of leprosy by Rodriguez and only twenty to the discussion of such an important disease of childhood as rheumatism and chorea by Gibson, although this latter chapter does not include rheumatic endocarditis, which is discussed by the same author in Volume III. Respiratory infections from a general standpoint have been handled by the editor, who also contributes a sane chapter, ''The Tonsil and Adenoid Problem,'' and one on the pleura, including empyema. The difficult subject of pneumonia is ably handled by Trask. The Jacksons have written on the larynx and allied topics, and Dean contributes the chapter on the nose and sinuses. The chapter, ''Surgery of the Thorax'' by Alton Ochsner, while excellent in itself, is in extent rather out of joint with the other chapters. The same holds true for the discussion, ''Helminths and Arthropods'' by Faust, and the chapters, ''Malaria'' and ''Tropical Diseases'' by Craig. These chapters are encyclopedic rather than personal in character. The volume ends with chapters on asthma, hay fever, and other manifestations of allergy by Schick and Peshkin.

Volume III (thirty-two chapters) is devoted to diseases of the alimentary tract, blood cardiovascular system, and urogenital tract. The more important chapters are ''The Acute Abdomen'' by Brennemann, ''Diabetes'' by Julian Boyd, ''The Anemias'' and ''Blood Dyscrasias With Hemorrhage'' by Cooley, ''Leukemia'' by Cooke, ''Acute Infections of the Urinary Tract'' by Helmholz, and ''Nephritis'' by Aldrich. A number of outstanding contributions from authors outside the field of pediatrics, as Vilray P. Blair, Millberry, Coe, F. J. Taussig, and Kretschmer, are included in this volume.

Volume IV (forty-two chapters) is given over to the nervous system, the skeletal system, and such miscellaneous subjects as arthritis, orthopedics, and diseases of the eye, ear, and skin. An introductory chapter to the nervous system, on basic considerations and neurologic examination, is contributed by Crothers. ''Encephalitis'' is written by Hempelmann, ''Meningitis'' by Levinson, and ''Epilepsy'' by McQuarrie. An excellent chapter, ''Disorders of Speech, Reading, and Writing,'' is contributed by Robert West. The chapters, ''Orthopedics,'' ''Diseases of the Eye,'' and ''Diseases of the Ear'' are excellent contributions by Chandler, Gamble, and Livingston, respectively, associates of the editor in his hospital work in Chicago.

The four volumes and index are constructed on the popular loose-leaf method of printing and binding, so that chapters may be easily revised and kept up to date. For this purpose each chapter begins with page 1, and each subject or topic constitutes a chapter. In all, the publishers state the System totals over 5,000 pages. The printing is good, and the editor and publishers are to be congratulated on the selection, excellency, and clarity of the illustrations. The publishers state that a ''*nominal* [our italics] annual service charge'' of $15 per year will be made for a threefold service of supplying revised pages for the System to replace those grown obsolete, for an ''international digest'' of significant current medical literature of the world, and a consulting bureau—files of abstracted literature being made available to subscribers. This yearly ''service charge'' we might point out amounts to almost 25 per cent of the original cost of the set. The last two items of the ''service'' are duplications in large part of what pediatricians are already receiving in their medical journals and with their society and library connections. We question whether the digest can equal the abstract and review departments of the current pediatric journals. Unless the publishers plan to replace many hundreds of pages of the present text of the system each year, the ''nominal annual service charge''

is decidedly out of line. It would seem in all fairness to the purchasers of the System that they should be allowed to obtain the revised pages at a fair price without the necessity of subscribing to the other services which they may not desire, or for which they have no use. The original cost amounts to slightly over one cent a page. On this basis the subscriber should be entitled to at least 1,000 revised pages a year, or one-fifth of the System, for the service charge of $15. No statement as to the number of revised pages to be issued yearly is made by the publishers.

B. S. V.

Surgical Emergencies in Children. By Harold Clifford Edwards, M.S. (Lond.), F.R.C.S. (Eng.). Baltimore, 1936. William Wood and Company.

Children, by virtue of their inherent mental and physical characteristics, are constantly becoming involved in situations which may result in surgical emergencies; and, while there are a few excellent works upon surgical conditions of childhood, handbooks for ready reference in this more limited field are conspicuous by their absence. The pediatrician, surgeon, or general practitioner who, confronted with such an emergency, wishes aid and counsel must usually thumb through a volume or search files of periodicals, to find only too often a compilation of opinions rather than a definite clear-cut course of procedure.

For those who have been in such a situation—and who of us has not?—this book will be a welcome library addition. The author gives the results of his own experience and observation, detailing tried and proved methods rather than presenting a general review. When a condition admits of several accepted lines of treatment, he has refrained from encumbering the text with them except on rare occasions when he may give an alternative method, stating that he has had no experience with it. This may be criticized by the advocates of certain procedures, but it gives to the one who is faced by the emergency the same assistance and comfort that would be derived from the personal opinion of a valued consultant.

In addition to treatment of the usual accidents and pyogenic infections, there are chapters dealing with acute, inflammatory, obstructive, and congenital abdominal conditions, with the thorax, and with the genitourinary tract. The chapters on anesthesia and on ear, nose, and throat were written by specialists in those fields.

A discussion of empyema is included in the chapter on the thorax, but the author remarks in extenuation that "it should not be regarded as an emergency in the strict sense of the word. A clear understanding of the pathologic anatomy has led to the abandonment of the onetime practice of operating on all cases as soon as the diagnosis is made."

The same careful regard for pathogenesis is evident in the discussion of appendicitis, appendiceal abscess, and osteomyelitis, the basic facts of surgical pathology being clearly and concisely presented as the determining factors in planning rational surgical procedures.

This is in no sense a textbook—adequate surgical training and judgment on the part of the reader being taken for granted, and conditions and reactions peculiar to infants and children being emphasized rather than elementary details of surgical technic and diagnosis. Occasional terms may be somewhat unfamiliar to the profession in this country, but the context is such that they are easily understood. The illustrations and text are clear. It is of convenient size and well indexed, making it an especially valuable handbook for quick reference. By consistent elimination of nonessentials and strict adherence to the subject (with rare self-control, even omitting the consideration of pyloric stenosis!), the author has succeeded admirably in producing a most readable book.

H. E. C.